FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

WEDNESDAY, JUNE 20, 2012

1:00 p.m. to 4:30 p.m.

Afternoon Session

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. WILSON: Okay. I'd like to go ahead and call the meeting to order. Just for the sake of time, let me just have the members that are new this afternoon, who are not present this morning, state your name into the record, and your specialty, and where you're from. And I think those of you who were here this morning can very briefly just say your name.

DR. BAYNES: Roy Baynes, hematologist, oncologist. I'm the industry rep and employed by Gilead Sciences in San Francisco.

DR. NEATON: Jim Neaton.

DR. MENEFEE: Michael Menefee.

DR. FOJO: Tito Fojo.

DR. BUZDAR: Aman Buzdar.

DR. WOZNIAK: Antoinette Wozniak.

DR. KELLY: Kevin Kelly.

DR. SEKERES: Mikkael Sekeres

DR. WILSON: Wyndham Wilson.

DR. BRIGGS: Caleb Briggs.

DR. FREEDMAN: Ralph Freedman.

DR. ARMSTRONG: Deb Armstrong.

DR. ZONES: I'm Jane Zones.

DR. OMEL: Good afternoon. I'm Jim Omel. I'm from Grand Island, Nebraska. I'm a retired physician. I also have had myeloma since 1997.

DR. WILSON: Would you please speak into the microphone?

DR. KOTI: Kallappa Koti, FDA.

DR. HERNDON: Thomas Herndon, FDA.

DR. DEISSEROTH: Al Deisseroth, FDA.

DR. FARRELL: Ann Farrell.

DR. PAZDUR: Richard Pazdur, FDA.

DR. WILSON: All right. Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without

interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

I'd like to remind everyone present to please silence your cell phones and other electronic devices if you have not already done so. The committee is reminded to please refrain from discussing the meeting topic during breaks. Thank you.

We now will have a conflict of interest statement read.

Conflict of Interest Statement

DR. BRIGGS: Thanks. I'd first like to identify the press officer, if you're here Erica.

(No response.)

DR. BRIGGS: I guess not.

The Food and Drug Administration, FDA, is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C., Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, FD&C Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These

interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

The agenda for this afternoon's session involves the discussion of New Drug Application, NDA, 202714, with the proposed trade name Kyprolis, carfilzomib, for injection, application submitted by Onyx Pharmaceuticals, Incorporated. The proposed indication or use for this product is for the treatment of patients with relapsed and refractory, recurring and/or not responsive to other treatments, multiple myeloma, who have received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent.

This is a particular matters meeting during which specific matters related to Onyx Pharmaceuticals' Kyprolis, carfilzomib, will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no

conflict of interest waivers have been issued in connection with this meeting. However, Dr. Julie Vose has been recused from participating in this session of the meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the issue being discussed today. With respect to FDA's invited industry representative, we would like to disclose that Dr. Roy Baynes is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Baynes' role at this meeting is to represent industry in general and not any particular company. Dr. Baynes is currently employed by Gilead Sciences.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such

involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue.

Thank you.

DR. WILSON: Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the

beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the sponsor's presentation.

Sponsor Presentation - Ted Love

DR. LOVE: Good afternoon. I'm Ted Love, executive vice president of R&D at Onyx. On behalf of my colleagues and our consultants, I'd like to thank the committee and the FDA for the opportunity to present data supporting the accelerated approval of carfilzomib for patients with relapsed and refractory multiple myeloma, who've exhausted other meaningful options.

Following my introductory comments, Dr. Ken Anderson from Harvard will discuss the unmet medical need in myeloma. Dr. Barbara Klencke and Dr. Natalie Sacks will then describe the efficacy and safety. Finally, Dr. Sagar Lonial from Emory

will discuss the benefits and risks of carfilzomib. Drs. Siegel and Packer are also here to answer your questions.

Carfilzomib has several unique features. Its proteasome inhibition is potent and prolonged, and unlike bortezomib, it's irreversible and highly specific. This produces less binding to off-target substrates, which eliminates peripheral neuropathy as a dose-limiting toxicity. Further, both preclinical and clinical evidence suggest that the increased duration of proteasome inhibition and the specificity of carfilzomib play important roles in overcoming resistance to bortezomib. The ability of carfilzomib to overcome bortezomib resistance has been studied extensively in preclinical models, including cells derived from patients with refractory disease.

Given that peripheral neuropathy is a major dose-limiting toxicity with bortezomib, it's important to understand that carfilzomib does not cause neurodegeneration. Let's take a look at the effects of these two drugs on differentiated

neuronal cells.

When neuronal cells are exposed to clinically relevant concentrations of either drug, only bortezomib, as shown in the center, induces neurite degeneration. On the other hand, due to its highly-selected mechanism, carfilzomib does not induce neurodegeneration. These findings are consistent with the lack of neurotoxicity seen in chronic dosing studies of animals.

Onyx has had multiple interactions with the Food and Drug Administration that have helped guide our development of carfilzomib. Our pivotal study 003A1 was modeled after the Velcade SUMMIT trial, which served as the basis for accelerated approval in 2003. Both were designed as single-arm studies for multiple myeloma patients who'd exhausted available therapies. We have extensively investigated carfilzomib. Our NDA submission includes data from nine phase 1 and 2 studies.

ASPIRE is a randomized phase 3 study in relapsed multiple myeloma, currently being conducted under a special protocol assessment with

the FDA. At nearly 800 patients, it's fully enrolled, however, we would not expect approval until 2014 or 2015. Onyx is also planning several additional phase 3 studies as part of our commitment to comprehensive development, including a superiority trial versus bortezomib, which is expected to start shortly.

Unfortunately, multiple myeloma remains a uniformly fatal disease despite significant recent advances. There are no treatment options with a favorable risk-benefit profile for patients who've exhausted available therapies, especially bortezomib and lenalidomide. Carfilzomib monotherapy can fill this void.

Carfilzomib is the first new myeloma drug to request accelerated approval based on single-agent activity since the advent of the bortezomib-lenalidomide era. Thus, the patients today are more advanced, refractory, and sicker than those in the historical literature. Drs. Anderson and Lonial will both address this.

Our goal today is to demonstrate that

carfilzomib safely addresses an unmet medical need. We intend to show that it achieves meaningful objective and durable responses at a level which is particularly notable for a single agent in such a heavily pretreated patient population. Its safety profile is well characterized and consistent across multiple studies and patient subsets. Finally, and importantly, it can be administered for prolonged durations without cumulative toxicity.

I would now like to introduce Dr. Ken Anderson to disgust the unmet medical need.

Sponsor Presentation - Kenneth Anderson

DR. ANDERSON: Thank you very much, Dr. Love.

I'm Ken Anderson from Dana-Farber in Boston. My time and preparation for this meeting has not been compensated, but my travel was supported. I'm here to frame the question this afternoon of the unmet medical need in multiple myeloma. And by way of starting out, I just wanted to show the historical picture of treatment of this disease, which really dates back to the 1960s. That's when

melphalan and prednisone was first introduced, and patients lived on average 2 to 3 years, before that time having died quite quickly.

In the 1980s and 1990s, high-dose therapy and stem cell transplant, first rescued by marrow and then by peripheral blood stem cells, came into being. And in fact, the median survival was on the order now of 3 to 4 years. Because of the prescient decision of the FDA nearly a decade ago, the first proteasome inhibitor, bortezomib, received accelerated approval in May of 2003, really starting the era of novel therapies in this disease. And the treatment para-time that has come since then has literally transformed how we think about and treat this disease.

Now, the prior proteasome inhibitor, bortezomib, as I just mentioned, was approved in May of 2003, accelerated approval, based on the SUMMIT trial. This and the next slide show you the characteristics of that single-arm, phase 2 trial in relapsed myeloma, in patients who were refractory to their last prior therapy, very

similar to those that you're going to hear about this afternoon. The primary endpoint was response rate.

As you can see on the right-hand side of this slide, these patients were very heavily pretreated with the agents and modalities that were present at the time. So stem cell transplant, as I just mentioned, steroids, alkylating agents, anthracyclines, were commonly used. Obviously, no one had had bortezomib, so there was no proteasome inhibitor exposure. And the IMiDs were very new at that time, so only a minority of patients had actually had exposure to that class of drugs as well.

Here are the results, the data upon which the approval was predicated. Namely, the overall response rate was 27 percent. If you look at the clinical benefit rate, it was a bit higher at 35 percent. The duration was quite significant, duration of response at 15 months and overall survival of 16 months in this trial.

So this did form the basis of the

accelerated approval. And then we've been very blessed in multiple myeloma. I'd like to just say I think the various constituencies represented in this room had a major role in all of this, especially the FDA. But with this accelerated approval followed a phase 3 clinical trial, which fortunately and very resoundingly supported the activity of this agent, and it's used very broadly in myeloma medicine today.

Now, here are the agents that we have available to treat this disease currently. There are many classes. The akylating agents are used throughout the course of treatment of patients with myeloma; anthracyclines. Pegylated doxorubicin, which is approved with bortezomib, is used primarily for relapsed myeloma. The nitrosoureas, which are approved, are very rarely, if at all, used nowadays. The IMiDs I've just mentioned are now used quite broadly across the spectrum of disease. And the proteasome inhibitor approved in an accelerated fashion in relapsed and refractory myeloma in 2003 was thereafter extended in terms of

its approval to relapsed myeloma, to upfront myeloma as well.

Now, these agents do all have side effects that are attendant to their use. On the other hand, there are also features that occur in patients that limit our ability to use these agents in particular clinical contexts. So virtually all of the agents, except for steroids, cause low blood counts. There's cardiotoxicity well known in the anthracyclines. Steroids, as well known, can cause hypertension or hyperglycemia, and the IMiDs, clotting and neuropathy. But for today's purposes, the only approved proteasome inhibitor, bortezomib, has attendant to its use neuropathy, GI disorders and low platelet counts.

So what do we do when we see new patients in the clinic? Which a number of us in this room continue to do and will do tomorrow as a matter of fact. We see patients with newly-diagnosed disease. We are blessed because we have the agents I showed you on the prior slide. We use combinations of targeted agents and conventional

treatments in initial, newly-diagnosed patients, and the survival can range from 20 to 50 months.

Unfortunately, the disease inevitably relapses, and we have FDA-approved options at that point, and we can achieve 14 to 16 months in terms of survival from that point. But why we're here this afternoon is, tragically, in virtually all patients, we get to what's called an unmet medical need, which is patients who have relapsed myeloma, which is now refractory to all agents or intolerant. In that setting, the patients live only a very short time on the order of 6 to 10 months.

In addition, patients start with morbidities such as neuropathy. And in fact, during the course of therapy, these morbidities can in fact increase, so neuropathy, marrow reserve, can in fact unfortunately limit our ability to use available agents, even in this setting. So we have not only refractory disease, but we have intolerance to available therapies.

So we can be all proud in this room of this

particular slide. On the left-hand panel it shows you what has happened to myeloma since the FDA approved bortezomib. The red line shows you that the median survival is now on the order of 5 years, markedly different than what it used to be before we had this first generational proteasome inhibitor. On the right-hand side of the slide, though, is unfortunately still the truth, which is, in fact, that with relapses, subsequent relapses, the response rate, but importantly on this slide, the survival is tragically quite short.

Now, when we look through the literature to try to get a metric or a framework upon which to base the data that you're about to hear about for carfilzomib, we found this paper by Dr. Shaji Kumar from the Mayo Clinic. It's almost 300 patients who had four lines of prior therapy, very similar to those that you're going to hear about here this afternoon. They had had their disease for over 3 years. And in spite of the fact that 31 different treatments were tried to treat these patients, unfortunately and tragically, the

survival overall was only 9 months.

Not only that, but those of you who attended ASCO in Chicago less than a month ago will remember this presentation from the International Myeloma Working Group, which is almost 400 patients. And this is probably the most current data you're going to see, from 2007 to 2010. But what it shows you is that with each subsequent relapse, the likelihood of response plummets. And so the patients that you're going to hear about in our 003A1 study are actually beyond their fourth relapse. So one would expect a very, very low response rate, indeed.

So what I've tried to paint a picture of here is although we can be very happy -- and, in fact, those of us who are caregivers and patients are incredibly grateful for the team that's represented in this room that's allowed the progress to take place over the last decade, and particularly the FDA -- I'm here to share with you that we still have an unmet medical need. There is no standard of care. There are few options for

patients who have relapsed and refractory multiple myeloma.

So what do we do when we see such patients? We put them on clinical trials, single agents or combinations. We do have transient responses but diminishing in terms of their duration. Their progression-free and overall survival is tragically very short. So we really do still need additional novel agents in this disease. We're always looking, as are you, for clinically meaningful responses. They need to be durable, and they need to have an associated clinical benefit. And hopefully this afternoon, you'll be convinced by the presentations to follow that carfilzomib represents a promising, next-generation proteasome inhibitor to meet the need in this clinical setting.

It's now my pleasure to introduce Dr. Barbara Klencke, who's going to talk to you about the clinical efficacy of this exciting agent.

Sponsor Presentation - Barbara Klencke

DR. KLENCKE: Good afternoon. I'm

Dr. Barbara Klencke from Onyx Pharmaceuticals. Today I will discuss the efficacy of carfilzomib from the phase 2 multiple myeloma studies. My main focus today will be the pivotal 003A1 study that was conducted in patients with relapsed and refractory myeloma. I will then briefly discuss the supportive phase 2 myeloma studies that provide additional evidence of carfilzomib's benefit.

I'll start with the 003A1 study. The single-arm, phase 2 study evaluated the safety and efficacy of carfilzomib in patients with relapsed and refractory myeloma. We utilized the International Myeloma Working Group definition for refractory status being that of progressive disease during or within 60 days of treatment, or stable disease as the best response to treatment. Specifically, this study required that patients be refractory to their last regimen received.

The 2008 ASH/FDA workshop on clinical endpoints in multiple myeloma described this population as one with a specific and clear unmet medical need. Patients with progressive disease

and measurable disease were eligible if they were refractory to their last regimen and had received all four classes of approved therapies unless contraindicated. The study permitted a wide range of patients to be enrolled, including those with high-risk baseline characteristics, such as poor performance status or evidence of organ impairment, as shown here.

Objective response rate as defined by the IMWG criteria includes the categories shown here. It must have been confirmed on two consecutive assessments and was identified or assessed by the independent review committee. Objective response, when durable and clinically meaningful, is an accepted endpoint for accelerated approval for patients with relapsed and refractory myeloma. Finally, the study was powered to exclude 10 percent as the lower boundary of the two-sided 95 percent confidence interval.

Among the traditional secondary endpoints shown here, you'll see the clinical benefit response. It incorporates minimal response in

addition to the standard criteria. Durable MR was agreed by the joint ASH/FDA workshop in 2008 to represent an important benefit to patients with refractory disease. And importantly, both MR and PR have correlated with overall survival and other measures of clinical benefit in previous myeloma trials.

The treatment regimen of carfilzomib monotherapy is given on 2 consecutive days each week, for 3 of the 4 weeks in a 28-day cycle. This study allowed therapy for up to 12 cycles. The consecutive-day dosing was shown in preclinical studies to produce deeper and longer proteasome inhibition and was associated with better activity. The dose in cycle 1 was 20 milligrams per meter squared given intravenously, and beginning with cycle 2, the dose was escalated to 27 milligrams.

This stepped-up dosing regimen, along with hydration and 4 milligrams of dexamethasone pre-medication was developed based on experience gathered in phase 1 and pilot phase 2 studies, and successfully improved the tolerability of the

regimen. Of note, the 24 milligram dose of dexamethasone given over a span of 28 days is sevenfold higher than standard low-dose dexamethasone, and 20-fold lower than high-dose dexamethasone given with therapeutic intent for myeloma.

Turning now to the demographic characteristics of this study, we enrolled 266 patients with substantial representation of patients over the age of 65 or of African Americans consistent with the epidemiology of this disease in the United States. At baseline, patients were on average 5.4 years from the time of their initial diagnosis, longer than in any other previously reported clinical trial. Ninety-seven percent were actively progressing at study entry. Ninety-four percent were confirmed to be refractory to their last regimen.

Both of these numbers were based on a central review, central confirmation, using standard IMWG criteria applied to laboratory data. This central confirmation was applied to ensure

robust compliance with the protocol design and to validate the treatment need of these patients. But I want to highlight that these percentages are conservative compared to the investigator, who also had the ability to incorporate additional data, such as radiographic evidence of progression.

The remaining data shown on this slide reflect the advanced disease state of these patients with multiple poor prognostic markers for outcome present at baseline, including high rates of anemia or other hematologic abnormalities, reflecting the poor marrow reserve in many. Patients received a median of 5 lines of therapy, often consisting of multi-drug combination regimens. Three-quarters of patients had undergone a stem cell transplant. And next, looking at the approved therapies, we see that nearly all patients had received bortezomib, an immunomodulatory drug, corticosteroids, and an alkylator, and 64 percent of patients had received an anthracycline.

The novel agents in particular were often given more than once, as they are commonly used

across multiple lines of therapy. The primary efficacy endpoint on the study, objective response rate as determined by the independent review committee, was 22.9 percent. This was associated with a robust median duration of response of 7.8 months. When we add in the patients with a minimal response, we see a clinical benefit response rate of 35.7 percent, also durable at 8.3 months.

This graph represents the duration of response for the 61 patients with a response of PR or better. Patients still receiving carfilzomib at the completion of 12 cycles were administratively censored at the time that they rolled over into an extension study. The analysis utilized standard IMWG criteria for progression, and based on the independent review committee's review of tumor assessment data, collected every four weeks.

Objective response was assessed and reported by the investigators, as well as by the IRC. And while there is variability between these methods, especially with the assessment of minor response or

complete response, the objective response rate was highly concordant across these methods.

In this forest plot, the response rate for the full 266 patients is shown at the top at 22.9 percent. The dotted vertical line at 10 percent signifies the prespecified lower boundary of the two-sided 95 percent confidence interval for response in the total population. Across all of these groups, there is generally a consistent benefit based on demographics and baseline disease characteristics, including patients with neuropathy or poor renal function at study entry.

The lower boundary of the 95 percent confidence interval is at or above the 10 percent threshold for nearly all of the subgroups, despite only powering the study to demonstrate this with the full study population. While survival data from single-arm study is difficult to interpret, the median overall survival was very encouraging at 15.4 months.

Now, I'll turn to a brief discussion of the

supportive phase 2 studies, which provide additional evidence of carfilzomib's activity.

In these phase 2 studies of bortezomib-exposed patients, most patients were both relapsed and refractory as they were in 003A1, which is included here for context. A similar response rate is seen across these studies at a range of doses, including doses lower than that studied in 003A1. In particular, the 005 renal impairment study was conducted because of the frequency of renal dysfunction in multiple myeloma. This study enrolled patients who were dialysis dependent, as well as others with moderate or severe renal dysfunction. Carfilzomib activity was preserved in these patients in whom treatment options are generally quite limited.

I will now turn to the bortez-naive but relapsed population enrolled in the 004 study. Response rates were significantly higher at 42 and 50 percent, depending on the carfilzomib dose tested. These data highlight the potency of carfilzomib and the consistency and reproducibility

of results across studies. In summary, these data demonstrate a durable and clinically meaningful benefit in patients with relapsed and refractory myeloma, progressing at study entry, who had exhausted available treatment options.

Carfilzomib achieved an objective response rate of 22.9 percent with a median duration of response of 7.8 months. A durable clinical benefit response was observed in 35.7 percent of patients. And carfilzomib's benefit was consistent across all clinically important subgroups. Moreover, the benefit is replicated in the supportive phase 2 studies. And together these data strengthen and support the conclusion that carfilzomib can benefit patients who have no remaining treatment options and thus have a critically important unmet medical need.

With that, I'd like to introduce Dr. Natalie Sacks from Onyx to talk about the safety of carfilzomib.

Sponsor Presentation - Natalie Sacks

DR. SACKS: Thank you. Today I'll be

covering adverse events, significant serious adverse events, including death and three areas of interest raised by FDA in its review: cardiac, pulmonary and hepatic.

Over 2000 patients have been exposed to carfilzomib, including 768 submitted in the NDA; 526 of these with advanced myeloma enrolled in multiple phase 2 trials. It's true that single-arm trials can limit the interpretation of safety data. Hence, I will provide relevant historical context, including that of bortezomib, the only approved proteasome inhibitor. I will also mention relevant safety data from the 1,000 patients enrolled in the ongoing phase 3 trials.

In the pivotal trial, patients received a median of 4 cycles or 4 months of treatment. One-third completed 6 of the planned 12 cycles, and 15 percent of these advanced patients completed 12 cycles of treatment. The grade 3 events in the pivotal trial were primarily hematologic, not unexpected in a patient population with preexisting blood dyscrasias.

What's important is that these laboratory abnormalities were rarely associated with clinical sequalae. Few patients had bleeding episodes associated with thrombocytopenia. There was a relatively low rate of opportunistic infections in patients with lymphopenia, and the key observation is that febrile neutropenia rate was only 0.8 percent.

Hematologic adverse events in general were not a common reason for discontinuation. Fatigue, constitutional, and gastrointestinal symptoms are the most common non-hematologic adverse events reported. The main observation is that the majority were low grade. Our experience in this and other trials indicate that no prophylaxis is required for nausea, vomiting or diarrhea.

You'll notice that peripheral neuropathy is not on this slide, and I'd like to discuss this further. Peripheral neuropathy, as you've heard, is not only a complication of myeloma but is also a drug-limiting toxicity with agents such as bortezomib and thalidomide. A 12 percent

neuropathy rate was observed, which represents a low rate of new onset neuropathy and a low rate of worsening of preexisting neuropathy. This is despite the fact that a majority of patients entered with baseline neuropathy. There were no discontinuations in the pivotal trial due to neuropathy. This is not an unexpected observation. These low rates are consistent with what was predicted by the profile of selective proteasome inhibition.

Here summarized is the standard safety endpoints across the multiple phase 2 trials. The pivotal trial is in the first column, and the entire phase 2 databases are reflected in the last column, which I'll emphasize when talking about less common events. What we see in general is consistency across the trials, and where differences do occur, these can be attributed to earlier- versus later-stage disease, as is seen in the 004 trial in relapsed but not refractory patients.

Only 12 percent of patients discontinued due

to adverse events, signaling the general tolerability of this agent in late-stage patients. These are the events that occurred at a rate of at least 1 percent in the pivotal trial. Not on this slide is the most common cause of discontinuation, which was disease progression in 60 percent of patients. At the end of 12 months, patients in the phase 2 trial were eligible to enter a long-term extension study. Of the 92 who enrolled, 78 received carfilzomib for at least a year, and 33 for at least 2 years, signaling a lack of cumulative toxicity.

Let's turn now to serious adverse events. Here we summarize SAEs both in the pivotal trial and in the entire phase 2 population. The majority of events are typical of the natural history of myeloma, such as pneumonia, acute renal failure, pathologic fracture, hypercalcemia, and spinal cord compression, and do often indicate disease progression. Also noted here is congestive heart failure, and I will turn now to the topic of cardiac adverse events.

Cardiac adverse events are common in patients with multiple myeloma for many reasons. Contributing factors include the presence of common cardiovascular risk factors due to advancing age, such as hypertension, diabetes. Factors due to myeloma include chronic anemia, amyloidosis, hyperviscosity, and prior exposure to cardiotoxic agents.

Importantly, there is a high incidence of cardiac morbidities in patients with myeloma. This slide summarizes the prevalence rates for various cardiac events in a claims database from United BioSource Corporation, in both newly-diagnosed patients and in patients who have received at least three treatments. As can be seen, congestive heart failure rates are 8 percent and 9 percent in these cohorts.

In the phase 2 trials with carfilzomib, there were three types of cardiac adverse events. The incidence of heart failure events was approximately 7 percent in this advanced myeloma population. Events related to cardiac arrhythmias

were in most cases clinically benign, consisting primarily of palpitations and changes in heart rate. Events related to underlying ischemic heart disease were uncommon. Discontinuation due to these cardiac events was infrequent with only 1.7 percent discontinuation rate due to congestive heart failure and a 1 percent rate for ischemic events.

To put this data in context, here is randomized data showing the incidence rates for heart failure observed with bortezomib and also the dexamethasone control arm in a clinical trial carried out in patients with less advanced disease.

The FDA has raised concerns that the cardiac events seen in the carfilzomib trials could lead to an excess of deaths. To examine this issue, it is important to consider the mortality experience in patients with myeloma. In a previous retrospective review of more than 3,000 patients, 10 percent died within the first 60 days of diagnosis, with about one-third of the deaths being related to a cardiac cause.

This slide shows the incident rates for on-study deaths in the phase 2 trials, defined as a death within 30 days of study drug exposure. A total of 37 patients, or 7 percent, died over a median follow-up of 4 months. The most common cause of death was disease progression. The other causes of death include those commonly seen with myeloma: infections, including sepsis and pneumonia, and also seen is the rare event of hepatic failure.

Of these 37 deaths, Onyx identified 8 events as being cardiac or having a cardiac component, whereas the FDA identified 10 events in the briefing book as being cardiac or having a cardiac component. Regardless of whether 8 or 10 events is used, it is apparent that less than one-third of the deaths appeared to have a cardiac cause, which is similar to the distribution seen in the 3,000-patient cohort study I showed in the previous slide.

We asked whether these cardiac deaths occurred primarily in patients with cardiac risk

factors prior to treatment with carfilzomib. Patients were considered in this analysis to have a cardiac risk factor if at baseline they were receiving one or more medications to treat non-cardiovascular conditions, such as hypertension or angina or heart failure. This table shows about 70 percent of the patients in the carfilzomib phase 2 trials had at least one cardiac risk factor. And not surprisingly, the cardiac deaths clustered almost entirely in this cohort, which you can see in the top row of the table.

If these cardiac deaths represented an excess risk, we would have expected patients who had a cardiac risk factor to have a higher mortality rate than patients who did not have a cardiac risk factor. Yet, the overall mortality rate in patients with and without such risks were similar, approximately 7 percent in each group, listed on the bottom of the table. This indicates that carfilzomib did not appear to adversely affect mortality rates in patients most likely to be susceptible to the occurrence of cardiac events.

Three deaths with a cardiac component were reported in patients who had received carfilzomib within the prior 48 hours. Careful examination of the individual circumstances in these three patients show that all three had significant preexisting cardiovascular disease, making it difficult to quantify the independent contribution of carfilzomib.

Finally, putting the overall mortality rate in context, this slide summarizes on-study mortality across clinical trials in relapsed and refractory patients. In the first columns, I've indicated what we observed in our trials, 9 percent in the pivotal trial and 7 percent across the whole phase 2 population. This uses the 30-day definition.

In the trial of lenalidomide, in a similar population, we see a 10 percent rate, and with the bortezomib trial used for accelerated approval, we saw a 5 percent rate, using a shorter definition of 20 days for on-study mortality. The bottom row notes time since diagnosis, with carfilzomib being

the most advanced. In summary, the causes and rate of deaths observed are comparable to that reported in the literature.

Lastly, let's turn to the adverse events of pulmonary and hepatic. Regarding pulmonary events, dyspnea was a common adverse event reported in 42 percent of patients; 5 percent were grade 3. One death was reported as due to dyspnea and occurred in association with congestive heart failure. The majority of dyspnea events were low grade and transient, with a median duration of 8 days, and discontinuations were infrequent.

To further characterize the dyspnea, we summarized the rates of important pulmonary adverse events and see generally low rates of such events in the table. I'll further note that there had been no adverse events indicative of interstitial lung disease, nor pulmonary fibrosis across the phase 2 database; nor have these events been reported as SAEs in the ongoing phase 3 trials. For context, these are reported rates of dyspnea in other multiple myeloma clinical trials. We see

agents with lower rates of grade 1/2 dyspnea, but similar or higher rates of grade 3 and 4.

Finally, I want to discuss hepatic events observed in our clinical trials. I'll start with the serious events listed in the top-half of the slide. This includes two patients with fatal hepatic failure who both had progressive disease at the time of the event, and one patient with reversible hepatic encephalopathy who was successfully rechallenged.

In phase 2 studies, discontinuations due to hepatic events were infrequent. In analysis of the laboratory database, no definitive case of Hy's law was identified across the entire safety database. What this means is that any lab abnormality, including those present in the adverse events just described, had confounding factors present. Importantly, in the ongoing phase 3 trials, which have enrolled close to 1,000 patients, there have been zero reports of hepatic failure as a serious adverse event.

In conclusion, the large safety database

provides a high degree of confidence in the safety profile of carfilzomib. Relapsed and refractory myeloma patients with multiple comorbidities can be safely treated with carfilzomib. There were low rates of discontinuation due to adverse events. Serious cardiac events and deaths were observed. They were observed at rates comparable to the literature. Carfilzomib can be used for long-term treatment in patients with peripheral neuropathy, which permits the opportunity for significant clinical benefit. And finally, no cumulative toxicity has been identified with chronic administration.

I'd like to now ask Dr. Lonial to speak regarding the overall benefit-risk.

Sponsor Presentation - Sagar Lonial

DR. LONIAL: Thank you, Dr. Sacks.

I appreciate the opportunity to be here. And what I'd like to do in the next few minutes is really try and bring together a lot of the material that you've heard in the last 30 minutes in the context of a clinical framework that I think we all

use as practicing clinicians to make decisions about risks and benefits when we're deciding about administration of a given therapy to patients with cancer.

So I'm going to start with a slide that you all saw earlier from Dr. Anderson. And in this slide, we really show what has happened in the last 10 years with myeloma therapy. And that's an improvement in overall survival. And what I like to describe is changing the natural history of multiple myeloma. And that really has been accomplished, as Dr. Anderson mentioned earlier, in collaboration between all the groups in this room, predominantly through the approvals of bortezomib and lenalidomide.

I want you to keep also close attention to the fact that all of the other curves, other than the red ones, are essentially overlapping and did not show significant improvement in overall survival over a decade worth of therapy, and are a consequence of the fact that these patients did not have access to proteasome inhibitors and IMiDs as a

therapeutic option.

So what do we have available when these agents are no longer functional or patients cannot take them; so when they're refractory to or intolerant to proteasome inhibitors and IMiDs? And this is what we're left with, the slide from 12 years ago, showing that with a median of 5 to 6 prior lines of therapy, overall survival is really quite short. And this is what I think we need to keep remembering, the idea that when patients no longer have access because of efficacy or tolerance to proteasome inhibitors and IMiDs, the existing exchange of drugs, whether they're corticosteroids, alkylators, or nitrosoureas, or anthracyclines, really do not do much to change the natural history and result in recycling of agents without significant clinical benefit.

Now, just to give you a short snapshot of what we do for some of these patients, obviously, we re-use these agents, use them in combinations. But these uses and combinations do not result in significant prolongation of progression-free or

overall survival, have very short duration responses, and in fact, these are actually very poorly tolerated. And this is another important point. We can recycle anthracyclines, or corticosteroids, or even alkylator agents, but their use comes with a significant price of morbidity. And that price of morbidity does not really result in significant long-term clinical benefit.

Clinical trials are obviously our first choice in this situation, and these clinical trials are what got us to where we are today with carfilzomib under consideration for approval. But unfortunately, a number of patients end up going on to supportive care, palliative care, or hospice care.

So, again, from a clinical perspective, let's think about the risks and benefits that need to be balanced in evaluating a potential drug. And so let's begin with the risk. And in my clinical mind there are three sets of risks that I like to know about when I'm thinking about administering an

agent for a patient with cancer. And the first is does this agent have toxicity that will preclude its efficacy? The second is what are risks that physicians and patients should be aware of? What can they expect when they receive this agent? And the third is, are there unexpected toxicities or AEs? And these three we're going to go through in the next few minutes.

So let's begin with the first one, really addressing the question of are there -- does toxicity of this agent preclude its efficacy? And as you can see here, if you look at bortezomib from the SUMMIT trial, lenalidomide in the relapsed and refractory experience, and then carfilzomib in the 003 trial, even though patients had similar median lines of prior therapy, the AE leading to discontinuation or drug-related AE leading to discontinuation was at least comparable between the carfilzomib 003 trial that we're talking about today and the two similar relapsed/refractory patient populations for bortezomib and lenalidomide, with one exception. And that is, in

the bortezomib and lenalidomide refractory patient populations, those patients had not been exposed to bortezomib or lenalidomide, whereas patients in the 003 trial that we're talking about today had been exposed to both classes of therapy as part of their disease treatment.

Now, what are the risks that physicians and patients should be aware of? Well, let's look again amongst different trials to get a sense for what the risks were in similar relapsed/refractory patient populations. And again, if you look at the SUMMIT and the CREST trials on the right and the 003 trial on the left, the incidence of any non-hematologic grade 3/grade 4 adverse events amongst these two trials were relatively similar. Again, remember, in the bortezomib experience, those were all proteasome inhibitor-naive patients, whereas everybody in the 003 trial had received a prior proteasome inhibitor.

There is one notable difference between these two, and that is the incidence of peripheral neuropathy. And just for those of you all who

perhaps do not see patients with myeloma or have to hear about the AE grading for patients with peripheral neuropathy, grade 1 means that it's a change in their baseline sensory function or motor function. And in most cases we're talking about sensory function here. Grade 2 means intefering with ADLs but not limiting their ability to do ADLs. Grade 3 means interfering with and limiting the ability to do ADLs.

So grade 3 clearly is a red flag. And as you can see here, the incidence of grade 3 peripheral neuropathy for carfilzomib-treated patients is quite low. But it's also important, from a patient perspective, to remember that grade 2 peripheral neuropathy is not a walk in the park, and that patients with grade 2 do have difficulty with ADLs, although they can continue to do it. And if they have painful neuropathy, that can be a lifelong comorbidity that they carry with them for the rest of their treatments. So management or minimalization of peripheral neuropathy with new treatments are something that I think is worth

considering.

So in the third category of toxicities are there unexpected toxicities? And this I think -- as we all think about clinical practice, this is one that we all really do pay significant attention to. And in all honesty, this cannot be completely excluded with the package that has been put before you today. There are 768 patients in the NDA database that you've seen. There are over 1,000 patients in the phase 3 trials that have been reported, and you have many of those AEs that have been reported through the FDA as well.

It is important to realize, though, that the ASPIRE trial, which is a randomized phase 3 trial, has been evaluated four times by the DSMB to date, which specific attention has to be paid for cardiovascular adverse events; and in an unblinded fashion has reviewed the data and has not issued any suggestions for change in the trial conduct. So I think that at least is a sense that people are looking in a randomized trial at potentially cardiac adverse events. And to date, we've not

heard any reason to change the trial as it currently exists.

So let's then switch to the on-study deaths. Again, this you saw from Dr. Sacks a few moments ago. If you look at the overall incidence, among 526 patients treated here. There is potentially a cardiac component in about 8 of those 526, for an overall incidence of about 1.5 percent. And just to put this, again, in perspective, compared to other trials, look at the incidence of on-study deaths between carfilzomib in the 003. The phase 2 experience, the lenalidomide in refractory/relapsed patients, as well as the bortezomib trials, again suggesting somewhat comparable incidences of on-study death, again with the caveat that while patients in all of these trials that I'm showing you here were relapsed and refractory, patients in the carfilzomib experience had been exposed to proteasome inhibitor and in IMiD, whereas the other two trials didn't necessarily have that; and, in fact, had had the disease for, on average, a year longer than the other patients, suggesting more

heavily pretreated and longer time since the diagnosis.

So now let's switch just for a moment about benefit. And this obviously is something that I heard earlier today, is not just a matter of numbers and P values. There needs to be some clinical benefit associated with this. As you can see, the overall response rate as assessed by the investigator, by the IRC for the trial, as well as by the FDA is 22.9 percent, suggesting reliability amongst all three sets of data, an internal consistency. And if you include the CBR rate, which includes minimal response, the CBR rate goes up to 35 percent.

This I think is worth mentioning. While I realize the FDA does not look at MRs and endpoint for a study, from a patient perspective, MR that was durable for 8.3 months does have some clinical benefit to it. And so I think it's worth not completely discounting that number, but at least realizing that that minor response was associated with a durable duration of remission.

So I think when we talk about benefits of carfilzomib, obviously overall response rate with durability and prolonged overall survival. You heard from Dr. Klencke early on today that the historical standard for overall survival in this patient population is between 6 and 9 months. In this trial, we showed an overall survival of 15 months, which again suggests there may be a change in the natural history for patients with relapsed and refractory myeloma that can only be confirmed in a larger, randomized phase 3 trial. I certainly grant that point, but it certainly is suggestive of important improvements in overall survival.

The risks of therapy are generally within what's expected for this patient population, a heavily pretreated relapsed and refractory patient population with good general overall tolerability, significant reduction in peripheral neuropathy compared to available agents. And as you saw from Dr. Sacks and Dr. Klencke, patients were treated far beyond a year, suggesting that there was not a

significant increase in cumulative toxicity over time with, again, promising overall survival.

So in closing, I'd like us all to keep in mind the idea that refractory multiple myeloma, with a median of 5 prior lines of therapy and 5.2 years since diagnosis, is a serious and life-threatening disease in and of itself, independent of the treatment that's administered to a given patient, which may obviously have its own risks and benefits. In this patient population, there is efficacy demonstrated with good tolerability and durability for a subset of patients. The safety does appear to be somewhat well-characterized. And in my opinion, the benefit-risk profile is somewhat favorable, supporting the use of carfilzomib in this patient population.

Just on a closing note, for those of you who are aware of the fact that the phase 3 trial is enrolled and accrued, and may be of the mind that, well, perhaps we should just wait for that phase 3 file rather than approving on accelerated approval

at this time, what I'd like to do is just a simple mathematical equation.

There are roughly 60,000 patients with myeloma at any given time, in any given year. And of those 60,000, roughly 10 [000] to 15,000 of them fit the entry criteria for the 003 trial that you saw presented today. If you wait 2 and a half to 3 years for that phase 3 trial, that's roughly 25 [000] to 35,000 patients that may not have access to this drug. And this is a drug that could potentially impact their duration of response and overall survival. And with that, I'll conclude. Thank you.

DR. WILSON: Okay. Thank you. We'll now turn to the FDA presentation.

FDA Presentation - Thomas Herndon

DR. HERNDON: Good afternoon. My name is Thomas Herndon. I'm a medical officer in the Office of Hematology and Oncology Products. I will prevent the FDA review for carfilzomib. The applicant is seeking accelerated approval for carfilzomib for the treatment of patients with

relapsed or refractory multiple myeloma, who have received at least two prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent.

This slide shows the FDA review team for this application. Here is the order of topics for the FDA presentation.

There are six major classes of drugs commonly used and approved to treat patients with multiple myeloma. These are glucocorticoids, alkylating agents, anthracyclines, nitrosoureas, immunomodulatory drugs, or IMiDs, and proteasome inhibitors. Throughout the course of the disease, patients are often retreated with the same drugs or other drugs from the same drug class.

This slide summarizes the drugs approved for multiple myeloma. Systemic therapy for multiple myeloma typically involves the combination of several of these drugs, often with corticosteroids. It is not unusual for a drug used as frontline therapy to be re-used in a new combination of drugs in a relapsed setting. Therefore, it is common for

patients with relapsed multiple myeloma to have received most of the drugs listed in the table on more than one occasion.

A previous approval, based on a single-arm study for patients with multiple myeloma was for bortezomib. The study was an open-label trial of 202 patients. Patients had received a mean of 6 prior therapies, and 64 percent of enrolled patients had undergone a stem cell transplant. The overall response rate for this study was 28 percent.

I will now discuss the efficacy results from the primary efficacy study. The primary efficacy study is PX-171-003-A1. From this point forward, I will refer to this clinical trial as Study 3A1. Study 3A1 was a single-arm trial. Carfilzomib was given at the 20-27 milligram per meter-squared dose, shown the slide. The study population must have received greater than or equal to 2 prior regimens for relapsed disease and progressed on the most recent therapy.

The primary endpoint for Study 3A1 was

overall response rate. The key secondary endpoint was duration of response. Study 3A1 enrolled a total of 266 patients from 31 sites in the United States and Canada. The median age was 63 years. Most of the patients were Caucasian, and three-quarters of the patients had an ECOG performance status of zero or 1.

Baseline disease characteristics are shown in the next two slides. Patients were heavily pretreated with a median number of prior therapies being 5 and a range of 1 to 20. Seventy-four percent of patients had had a stem cell transplant. Ninety-five percent of patients were refractory to the most recent therapy. The patients were extensively exposed to approved chemotherapy prior to study enrollment. Close to 90 percent of patients were documented to be unresponsive or intolerant to bortezomib and lenalidomide.

The results for the primary endpoint overall response rate are shown. There was one patient who had a complete response, 13 patients who had a very good partial response, and 47 patients who had a

partial response. While there may be some differences between the results obtained by the internal review committee and investigators, these did not affect the overall response rate.

FDA determined the overall response rate for groups of patients unresponsive or intolerant to different combinations of approved therapies, while the total number of patients for some of the groups was small, the overall response rate remains in the same range, approximately 22 percent for all groups. Duration of response, defined as the time from first response to the time of disease progression, was 7.8 months.

Carfilzomib infusion is associated with a number of adverse events. Dexamethasone was required prior to each administration of carfilzomib in cycles 1 and 2, and was optional thereafter to decrease the severity of these adverse events. This would result in a dose of 24 milligrams of dexamethasone per cycle for at least the first two cycles. Dexamethasone is typically given at higher doses for the treatment

of patients with multiple myeloma.

To summarize the FDA efficacy review, the overall response rate for Study 3A1 is 22.9 percent. The median duration of response is 7.8 months.

I will now present the findings of the FDA safety analysis. As it is difficult to attribute adverse events in single-arm studies, this slide depicts some of the pertinent toxicities observed in the non-clinical studies. Studies of carfilzomib in rats and monkeys resulted in deaths due to multiple cardiac and pulmonary toxicities.

The safety population, analyzed by FDA, consists of the 526 patients with multiple myeloma enrolled in single-arm, phase 2 studies. The majority of these patients were in the primary efficacy study, Study 3A1. As the safety data is based on phase 2, single-arm studies, it is difficult to determine if the adverse events are due to the drug, to pretreatment comorbidities, or to treatment history.

The dosing of the phase 2 safety population

is depicted in this table. The majority of patients received the 20-27 milligram per meter squared regimen, 38 percent of patients received a lesser dose, and 10 percent received a different dosing schedule. The demographics and baseline characteristics of the safety population were similar to the study population for the primary efficacy study.

On-study deaths were defined as occurring within 30 days of the last dose of carfilzomib. There were 5 deaths, where cardiac events were treated as the primary cause of death by both the applicant and the FDA. An additional 2 cases were associated with a cardiac cause of death, and in 3 more cases, cardiac events may have played a role in the cause of death. In addition to the deaths associated with cardiac causes, there were 2 deaths that attributed to hepatic failure. The majority of the on-study deaths occurred in the patients enrolled in the primary efficacy study, Study 3A1.

The second and third leading causes of discontinuations, secondary to adverse events, were

cardiac and pulmonary events. The number of cardiac and hepatic deaths and discontinuations due to pulmonary causes prompted additional analyses, which I will discuss in the next several slides.

Regarding the pertinent cardiac adverse events, there were 7 on-study deaths attributed by the applicant and/or the FDA to cardiac causes and 3 additional cases where cardiac adverse events may have played a role in the cause of death. A review of the medical history of these 10 patients showed that 9 of them had previous coronary artery disease or cardiac risk factors. Forty-two patients had a cardiac serious adverse event, 30 patients discontinued carfilzomib due to a cardiac adverse event, and 9 percent of patients had cardiac adverse events that were grade 3 or greater in severity, the most common being cardiac failure, congestive, and cardiac arrest. Because the data is from single-arm studies, attribution of the adverse events is difficult.

There was one on-study death attributed by the applicant to dyspnea. FDA attributed this

death to heart failure. Thirty-six patients had a respiratory serious adverse event, 22 patients discontinued carfilzomib due to a respiratory adverse event, and 11 percent of patients had respiratory adverse events that were grade 3 or greater in severity, the most common being dyspnea. Again, because this is data from single-arm studies, attribution of the adverse events is difficult.

There were 2 on-study deaths due to hepatic failure. Both of these patients had normal liver laboratory tests before receiving carfilzomib. There were 3 other life-threatening cases of hepatic failure that, in contrast to the above 2 cases, were reversible. There were no Hy's law cases.

To summarize the FDA safety findings, life-threatening cardiac, pulmonary, and hepatic adverse events were seen in a small percentage of patients with relapsed or refractory multiple myeloma. Single-arm trial designs confound the attribution of adverse events. It is not clear what role the

disease, previous therapy, or the study drug may have played in the adverse event profile.

These were the major ongoing or planned randomized trials at the time of the NDA submission. Study PX-171-009, a confirmatory trial for which FDA granted a special protocol assessment, is a randomized, multicenter, phase 3 study, comparing lenalidomide plus dexamethasone, with or without carfilzomib, in patients with relapsed multiple myeloma. The primary endpoint is progression-free survival. This study has completed accrual. Study 2011-003 is a randomized, open-label, phase 3 study of carfilzomib plus dexamethasone versus bortezomib plus dexamethasone in patient with relapsed multiple myeloma, with the primary endpoint being progression-free survival. Enrollment will begin in June 2012.

In conclusion, the overall response rate for the primary efficacy study was 22.9 percent. The median duration of response was 7.8 months. Life-threatening adverse events were seen at low frequency in single-arm trials among heavily

pretreated patients.

The FDA question for the ODAC is has a favorable benefit-risk profile been shown for the treatment of patients with relapsed or refractory multiple myeloma, who have received at least two prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent?

Clarifying Questions from Committee

DR. WILSON: Okay. Thank you very much. We will now proceed to questions from the committee to the sponsor. For those of you who have not been here before, the way we do this is you raise your hand. Caleb puts your name on the list here, and we go forward from there.

Let me just ask you a couple of questions. I think that one of the issues for me is how this drug stacks up to bortezomib. And the definition of refractory, at least in my field, is a little loose in the myeloma world, but that's neither here nor there. I'm wondering whether or not you can tell me the following.

Among those patients who received bortezomib

as their last therapy and progressed on bortezomib, what was the response rate of this agent?

DR. LOVE: So your question is what is the response rate in patients who previously or immediately progressed on bortezomib?

DR. WILSON: Not previously but was their last regimen. I don't want bortezomib that was given four regimens ago for which they had stable disease or came off because they had peripheral neuropathy. I'm trying to get a sense of how does this stack up against bortezomib. I mean, obviously, the cards are stacked against you because they had a lot of other therapy, but I'm just curious whether or not you looked at that.

DR. LOVE: I'd like to ask Dr. Klencke to address that.

DR. KLENCKE: Slide up, please. This has a number of different points on it, but it does explore prior bortezomib in a number of different ways. So to orient us, on the top are all the patients who received bortezomib, all but one. The next bucket, number of bortezomib regimens, more

than 2 and just a bit over half.

So the next line is pertinent, received bortezomib; in the last line, 132 patients, so exactly half of the group. And then refractory to bortezomib in the last line -- in fact, many of the patients who received bortez were refractory, 120 patients. Their response rate was 18.3 percent and the confidence intervals as shown.

DR. WILSON: Thank you very much. That's exactly what I wanted.

Dr. Kelly, did you have a comment or question about some items?

DR. KELLY: Yes. Just a clarification. You allowed patients with stable disease on the trial. Is that correct?

DR. LOVE: The patients, when they entered the study, were all progressing. That was a requirement for a patient.

DR. KELLY: Okay. So they were all progressing.

DR. LOVE: Correct.

DR. KELLY: All right. The other question I

have -- can you put up the trial design of the ASPIRE trial, so we can actually see it? The confirmatory trial.

DR. LOVE: I'll ask Dr. Klencke to describe the design.

DR. KLENCKE: Slide up, please. This is a trial of relapsed not necessarily refractory patients. Patients must have had a prior regimen, 1 to 3 prior therapies required. The sample size was 780 patients were stratified for prior bortezomib, prior lenalidomide, and beta-2 microglobulin levels. And it's lenalidomide and dexamethasone with or without carfilzomib.

DR. KELLY: Thank you. Next question. Seventy-seven percent of the patients had baseline neuropathy. How was this monitored throughout there? There are multiple tools you can use. Was this just an investigator's assessment, or did you have special tools that you used for monitoring neuropathy?

DR. LOVE: So, again, to confirm, your question is how was neuropathy monitored throughout

the study conduct?

DR. KELLY: That is correct.

DR. LOVE: I'd like to ask Dr. Sacks to address this.

DR. SACKS: Slide up, please. In answer to your question, this describes how the study was executed. So first, history and baseline status were established, obviously prior to study drug exposure. And then throughout the study, it was specified per protocol to do physical exam with special attention to a prespecified neurologic exam on day 1 of cycles 3, 5, 7, 9 and 11. And at the end of this study, we also collected all adverse events and reconciled these with the neurologic exam to arrive at our assessment of the neuropathy rates.

DR. KELLY: So the patients who had neuropathy to begin with, do you have a graph that's showing if there's any change in the scoring afterwards? So those with grade 1 or grade 2 on entry, do we have data on that?

DR. SACKS: Slide up, please. So just to

clarify, there was not a scoring system. But what I do have is data that shows what happened to patients, based on their baseline neuropathy status. You can see at entry, 378 of the patients in the phase 2 database across those trials had baseline neuropathy of grade 1 or 2; 147 did not. And then you can see the rates reported by those two groups, with the 12 percent in those that had neuropathy and the 17 percent who did not.

DR. WILSON: So I just wanted to give Onyx the opportunity to address a letter that we received from a Dr. Singhal, which makes statements about there being some disagreements between himself and the independent review committee -- and of course, Onyx was following the independent review committee -- regarding responses.

From my perspective, most of the significant changes in responses had to do with minor responses, which isn't what we're really focusing on here. But a lot of it was contingent on what the duration of response was, whether or not you started the clock at the last evaluation when there

was a minor response, or if you -- I mean stopped the clock, or if you stop it when you see disease progression.

So just to kind of get the air clear, I'd like to give the company an opportunity to simply address this, and FDA as well.

DR. LOVE: Thank you for the opportunity, Dr. Wilson, to address this. We certainly respect Dr. Singhal's looking at the data carefully, but, in fact, this is exactly why one has an independent review committee, so that a group of experts can come in and independently review the data, recognizing there can be differences of opinion.

We have looked at this data, as has already been pointed out, through a number of ways. So as Dr. Klencke mentioned, when you look at the response rate, which is the primary endpoint under consideration here today, the response rate, or ORR, is approximately 22 or 23 percent. Even with the methodology that Dr. Singhal has used, the response rate is 22.9 percent. There were, as you can see, differences around minor response, but

minor response is not the primary endpoint.

DR. WILSON: Does FDA have any comments?

DR. DEISSEROTH: Yes. It's clear that there's remarkable alignment between the analysis conducted by the IRC and the company and the FDA analysis. With respect to overall response rate, we looked at overall response rate in many different ways. And as Dr. Herndon outlined, we always came up with 22, 23 percent.

We also looked at the communications from the investigator, and it is our opinion that the issues that are alluded to by the investigator does not change the prespecified endpoint for the primary trial. And so we don't see any relevance for discussing that issue further.

DR. WILSON: Well, thank you. That was certainly my take on this, but I wanted to bring it to rest for the committee. So let's move on.

Dr. Menefee?

DR. MENEFEE: So I actually have two questions. The first is with respect to the cardiotoxicity observed in the study. The

information provided suggested that I guess about a third of patients had no prior anthracycline exposure. So I'd like to know was there any difference in the rate and/or severity of the cardiotoxicity in anthracycline-naive patients as compared to patients with prior exposure to anthracyclines?

That's the first question. I don't know if you want to take that.

DR. LOVE: I'd like to ask Dr. Sacks to address this. The question relates to risk for cardiovascular events relative to prior exposure or not, of anthracyclines.

DR. SACKS: Excuse me.

(Pause.)

DR. SACKS: I do not have a specific breakdown of patients with prior exposure to anthracycline or not. And then associated with cardiac adverse events on study, we did look at anthracycline exposure in our analysis of the cardiac deaths with 10 patients we were discussing earlier.

Slide up, please. And just pointing you to the bottom of this slide, of which is a list of factors that we compared, looking at the 10 patients with a cardiac component to their death as compared to the entire phase 2 population, you see a 40 percent exposure in the first column and a 53 percent exposure. So in fact slightly lower. I can't comment on whether that's statistically significant. So that exposure did not seem to carry a particular weight, at least in the assessment of cardiac deaths.

I will note that the anthracycline use in multiple myeloma is at doses that are a bit lower than in the solid tumor setting.

DR. MENEFEE: Thank you. And so my second question relates to prior therapy. I'm not a myeloma person, but I guess recently the paradigm has been shifting so that more patients have been getting maintenance lenalidomide or immunomodulatory therapy, post-transplant or after the first-line setting.

So I wanted to know was that patient

population represented in this study. And if so, were there any differences in response rates in those that were getting maintenance therapy as compared to those who were getting more traditional treatment?

DR. LOVE: So the question is really about whether or not patients were coming into our therapy on maintenance lenalidomide and whether or not -- could you ask the question again? I want to make sure we understand it.

DR. MENEFEE: Yes. That's essentially it. Were there patients who had received maintenance lenalidomide, or thalidomide for that matter, on the study; and if those patients were present, was there any difference is response rate?

DR. LOVE: I'd like to have Dr. Klencke address this.

DR. KLENCKE: I think because of the era in which this study was conducted, lenalidomide, as you say, is now being used frequently in the first-line setting as a maintenance therapy. CALGB study has shown an overall survival advantage.

Other large studies have shown a PFS advantage. That's rather new data in the last year, and I believe that data might be under review or is to be submitted.

But in our patient population, with 5.4 years since the time of diagnosis, I am not aware of any patient in our study that did receive maintenance with lenalidomide in first line. You raise one interesting small point, though. That is, when I say patients had a median of 5 lines of therapy, some of these lines of therapy are quite complex. They can include induction, consolidation, maintenance, and all of that being deemed one line of therapy. But I'm not aware that we had any long-term lenalidomide maintenance.

DR. WILSON: Okay. Thank you.

Dr. Neaton?

DR. NEATON: Thank you. I have a few questions on your efficacy endpoint. And maybe you could put up slide 15 just kind of for reference purposes, that we looked at a few minutes ago.

So as I understood the presentation and

Appendix 1 in your report -- essentially laboratory measurements, because they're largely based on serum and urine to do this classification -- they were performed every 4 weeks?

DR. LOVE: Yes.

DR. NEATON: And then to meet one of these categories, it had to be confirmed.

DR. LOVE: Correct.

DR. NEATON: And so if I come in at 4 weeks and I'm classified as MR, and that's confirmed, but then I come back 4 weeks later, and I go to PR, and that's confirmed, where do I get counted?

DR. LOVE: I'd like to ask Dr. Klencke to address that specifically.

DR. NEATON: And maybe kind of related to that, I didn't get any sense in these analyses what the time frame we're talking about is here. This is the patient's status at any point, the best status at any point during the follow-up, or is it at some specific follow-up time point?

DR. KLENCKE: This is best response during their entire duration of study therapy.

DR. NEATON: So this is the best that they did through any point in therapy.

DR. KLENCKE: That's right. And, as we say, the duration of partial response was 7.8 months. Median duration of minor response or better was 8.3. And it was two consecutive assessments required.

DR. NEATON: Do you have this table -- for example, you said the median number of cycles was 4. Can you show us this table after, say, 4 or 6 months?

DR. KLENCKE: Actually, I don't have a table defining response by cycle. The time to response, the median time to response was 1.9 months.

DR. NEATON: When you say response, though, is that the best response on this table?

DR. KLENCKE: Ah. Good point. So if we look at median time to a partial response, a partial response did require two assessments, but when we talk about median time to onset of that response, that's the 1.9 months. So we would count the time to response as the first of the two, but

we would only count it if that patient then had confirmation at the very next time point.

DR. NEATON: And that's 4 weeks later.

DR. KLENCKE: That's 4 weeks later.

DR. NEATON: So I guess where I'm going here is that the more you do this, the more opportunities you have to kind of --

DR. KLENCKE: That's true.

DR. NEATON: -- to move. Is this a comparable scheme that was used, for example, in the studies of the other drug? Because otherwise, you're comparing apples and oranges.

DR. KLENCKE: Yes. And I'm happy to have Dr. Lonial or Dr. Anderson speak to the frequency of study assessments. But I think that's why the durability is an important measure in this study.

So maybe, Dr. Anderson, you can speak to how frequent tumor assessments are often done in clinical trials.

DR. ANDERSON: Yes. I think this is a very prescient point because the more frequently you look, the more you may find. And so with that in

mind, we've had actually workshops in the past with the FDA, trying to define metrics of success, et cetera. We more recently have been blessed -- we have the International Myeloma Working Group, not unlike what exists in lymphoma, where we've actually standardized those categories of response that you saw and the blood and urine measurements that are required to meet those metrics, as well as the confirmation, as well as the frequency.

So those actually -- many of the large trials that you've heard about here today do have this very same design.

DR. NEATON: Every 4 weeks, with confirmation.

DR. ANDERSON: Yes.

DR. NEATON: Because, I mean, it's obviously, as you're indicating, a function of the laboratory era in those measurements. It's largely laboratory measurements that you're using, to come up with these classifications.

DR. ANDERSON: Yes. I totally agree. And

this is really an international effort now, which was really essential if we're going to try to compare novel agents compared to what we already have. So I think it's a very good point.

DR. NEATON: And just to make one other question. Did I understand that you report correctly that this is the best, but that virtually all but 11 of the patients progressed?

DR. KLENCKE: There were patients who had progressive disease as their best response. We actually tested tumor assessment measurements on day 15, and then started the monthly. How many patients were progression-free at the end of the 12 cycles? Eleven patients did roll over to our extension study and who were still progress-free at that point.

Maybe I'll show you my duration of response. That's the --

DR. NEATON: I'm referring to page 39 of the report, where I understood 11 people out of the 61 responders had not experienced progression. So I assumed all the rest had, during the time frame of

this study.

DR. KLENCKE: So 11 of the 61 responders had not experienced progression or had not initiated a new therapy at the time of the NDA cutoff. Eleven of those patients entered the long-term extension study to remain on carfilzomib. The others were censored.

DR. NEATON: I think the corollary of that is that all of the other patients --

DR. KLENCKE: Yes.

DR. NEATON: -- except the 11 progressed.

DR. KLENCKE: Yes.

DR. WILSON: So I think it's worth saying that this is very standard, and I think that -- you know, I think you make a very good point. And that is that response alone doesn't really tell the story; it's a surrogate. And it's really the duration of response; that is, how long are people presumably not having their disease worsening, at the very least, and that would be progression-free. But duration of response would be among those that are responding. So I think the numbers here look

to be fairly robust, but I don't think there's anything odd about how the timing for these responses are done.

Dr. Wozniak?

DR. WOZNIAK: One of my questions was already answered with regard to the anthracyclines. But I wondered, were patients who had amyloidosis allowed on the trial?

DR. LOVE: No.

DR. WOZNIAK: No. Okay. I just wondered if there was a connection between the presence of amyloid and the cardiac issues, as well as the hepatic toxicity. It's unknown, right?

DR. WILSON: Would it not be more fair to say that those with overt known amyloidosis weren't allowed on the trial, but certainly there could have been amyloid deposits within the cardiac conduction systems?

DR. WOZNIAK: I just had one more question.

DR. WILSON: Oh, yes. I'm sorry.

Dr. Wozniak?

DR. WOZNIAK: Just one more question. In

terms of the patients who have the hepatic toxicity, the 2 patients, were there any other conditions that could have contributed to them? For instance, were they on statins? Were there other medications?

DR. LOVE: There were, and I'd like Dr. Sack to take you through those.

DR. SACKS: Slide up. This does show very brief details on the two patients that you're speaking of. So two gentlemen, each about 70, were both heavily pretreated. And you can see there the day of their hepatic death, unfortunately, the time since last dose. And what you're referring to in the last column is potential confounding factors of progressive disease, multiple hepatotoxic concomitant medications. And of note, clinically in both cases, there was a picture that was consistent with hypoperfusion and liver ischemia, which itself can cause hepatic failure.

DR. WILSON: Okay. Thank you. Dr. Omel?

DR. OMEL: My question was also partially answered. The key study criteria explains that

patients with active cardiac disease were excluded. Can you explain to us how active cardiac disease was defined? And more importantly, outline which myeloma patients should be excluded from using carfilzomib if it is given accelerated approval?

DR. LOVE: I'd like to ask Dr. Sacks to address both of those questions.

DR. SACKS: The guidance we would provide would reflect the inclusion criteria in the trial, which I think you're referring to. So that included New York Heart Association, class 3 and 4 not permitted, NYHA 1 and 2 permitted. So that would be our recommendation. In addition, symptomatic ischemia was excluded, myocardial infarction within 6 months, and conduction abnormalities not adequately controlled with conventional intervention.

So that's the protocol exclusion criteria, and it would be our recommendation that that would be the guidance going forward.

DR. WILSON: Okay. Thank you. Dr. Fojo?

DR. FOJO: So maybe I'm looking at this a

little bit differently. Since it's a phase 1 -- I'm sorry. Since it's a single-arm study, it's important to think about some of these things. You had the comparison in the -- what was provided to us, to this review by Kumar, et al., and I think that that has a problem in it the way that you have it. Actually, Dr. Anderson had the correct number on it, which was 3.3 years from the time of diagnosis. Somehow in there, you ended up confusing the median estimated follow-up with the time to diagnosis. And you put that in there of 5.8 years, and had it as comparable to your 5.4 years.

So I'm not quite sure that the Kumar data is a good control. The reason I say that is because I think that if you're doing a study -- this isn't about patient population. They've been on treatment for 5.4 years and have had a median of 5 regimens. They've already declared themselves as having indolent biology to their disease. I mean, this is a good patient population. Dr. Anderson had survivals of 20 to 40 months, and then also

mentioned 5 years. These patients' median survival isn't 5 years. It's way beyond 5 years, as you well know.

So because of that, I'm not quite sure that then the duration of response is all that meaningful, because once you get a response, if you've had indolent biology, you're going to have a long duration. I think that we -- in fact, there's data in here because you show for the overall response -- the median duration of response is 7.8 months. And then when you add the MRs in, which is half as many, it goes up to 8.3 months. That tells you that the MRs had a much, much better median duration of response. In fact, maybe if I was getting the drug, I'd want to be treated to an MR and then stop, because that's going to be the best outcome.

So I think that the duration of response is probably driven largely by the biology of these patients that have been selected. So consequently -- then I think the response rate really is an important parameter. So then you had

shown Dr. Wilson the data with bortezomib refractory, but how many of the patients are bortezomib intolerant and one of those responses is being counted -- and one of those treatments is being counted as -- how many really had bortezomib?

DR. LOVE: So what you'd like to see is data on patients, whether they were bortezomib refractory or bortezomib intolerant?

DR. FOJO: Intolerant. Correct.

DR. LOVE: Dr. Klencke can tell you this information.

DR. KLENCKE: And before I show you the bortezomib refractory and intolerant information, to make a quick comment about the duration of patients with an MR or better, being a little bit better, they actually had on average a faster time to onset; that is, the median time to minor response was 1 month. The median time to partial response was 1.9 months. Most patients, as they declined in their serum or urine and proteins, went through a phase of a minor response first. So the additional time happened to be on the front end.

Could I have this slide up? This shows proportions of patients who are exposed refractory, intolerant, both, or neither. So look at the first row here. And what this shows is that 73 percent of patients were refractory; 42 percent were intolerant; 26 percent were both refractory and intolerant; and 11 percent were neither. And I think I did the math the other day to look at the difference between those who were intolerant but not refractory. And instead of 42 percent who are intolerant, it dropped to 16 percent because there is considerable overlap between those who are refractory as well as intolerant.

DR. FOJO: But if we remove the intolerant out of it, then what is the response rate in those who have had prior bortezomib and are truly refractory? So a good dose of bortezomib; not that they quickly become intolerant and didn't have a good trial of bortezomib.

DR. KLENCKE: So we had a slide up earlier, where we looked at the bortezomib activity. And I'll just take a moment.

Slide up. This one is looking at patients who are refractory to bortezomib in any prior regimen. Their response rate was 16.5; confidence interval, 11.6 to 22.5; duration, 7.8 months.

DR. FOJO: Okay. So this still doesn't answer it, so maybe you don't have it broken down that way. So maybe --

DR. KLENCKE: Well, there's no intolerant -- so this is -- I have other numbers that were refractory and/or intolerant. This is refractory only. What I don't have for you is the response rate in the 16 percent of patients who were intolerant but not refractory.

DR. WILSON: So, Tito, this is the very first question I asked.

DR. FOJO: Correct.

DR. WILSON: This is refractory only.

DR. FOJO: Right.

DR. WILSON: This doesn't include intolerant.

DR. FOJO: Correct.

DR. WILSON: This is received as the

last -- as most recent regimen. Now, the only thing that you could argue about is that they call refractory, progression within 60 days. Now, that happens to be what the myeloma people do.

DR. FOJO: Right.

DR. WILSON: I personally -- in lymphoma, we would never do that. We would not consider those people refractory. But the fact is that's what the criteria is, and that's what the myeloma community does.

DR. FOJO: Just one question to Dr. Anderson. What would he expect the response to bortezomib to be in this patient population; zero, 10?

DR. LOVE: I think I'm going to invite Dr. Lonial to come up and address the last topic.

(Laughter.)

DR. LOVE: Okay. Dr. Anderson has volunteered.

DR. ANDERSON: You get the older version, but perhaps Sagar can also comment. I think in the truly bortezomib refractory, retreatment with

bortezomib, as a single agent or with dexamethasone, none. But your point does raise that you can, with proteasome inhibitor, treat with combinations and sometimes overcome resistance. And there is data here that these patients receive bortezomib multiple lines of therapy and often in those combinations with pegylated doxorubicin, et cetera.

So I think that bortezomib refractory -- and as Wyndham says, it is defined, right or wrong, as growing on bortezomib or within 60 days, of stopping it. But the answer precisely to your question, Tito, is that you would expect a very low response rate in true bortezomib refractory patients as defined.

DR. FOJO: Okay. And then I had one other question with regard to your CS-10, and it has to do with tolerability, because -- your slide CS-10, carfilzomib long-term extension study.

So 92 patients were enrolled into the extension study. What is the denominator here? That's not just off of the trial here. That's your

total carfilzomib experience, right?

DR. LOVE: Okay. Dr. Sacks?

DR. SACKS: The denominator here, the patients who are eligible were those who completed -- the protocol prescribed 12 cycles of treatment in any of the previous or existing protocols.

DR. FOJO: So it might be that 768 number or something like that.

DR. SACKS: Yes. With respect to myeloma, it's the 526 patients in the phase 2 trials.

DR. FOJO: So the reason I asked this is because -- so I'm not quite sure that it's fair to say, oh, this is well tolerated long term because, obviously, you end up taking it long if you tolerate it at some level, and it represents only a small fraction of the patients.

I say that because in this study, remarkably, they had very little duration of treatment. It was 4 to 5 months. So what we really have is toxicity for a 4- to 5-month period of treatment. And I would think that in the

upfront setting, that might be a lot longer, and then maybe the toxicity might be different. I suspect you would probably --

DR. SACKS: I'd like to make one clarification. So the 4 months of average exposure, the primary reason that the patient stopped is progressive disease, not adverse events. So just a minor clarification there.

DR. FOJO: Right, right. No, I understand that. I wasn't saying --

DR. SACKS: But you're making a fair point about --

DR. FOJO: Exposure.

DR. SACKS: -- what to conclude in the long term. And here we were just trying to demonstrate, for these end-state patients with significant comorbidities, that there were patients who are able to tolerate treatment for quite a long time. Your point is very fair.

DR. FOJO: Okay. And then the one last thing, which is alluded to -- I mean, there does seem to be a dose response. The numbers are small,

but 27 seems to be better than 20. You all say that.

DR. SACKS: Yes. We did not make formal comparisons, but I'll ask Dr. Klencke --

DR. KLENCKE: I would like to show you two pieces of information about the dose response. Slide up. We performed pilot portions of 003 and the pivotal portion of 003 with different doses but identical patient population. Similarly, the 004 study initially started with a 20-milligram dose, and then was amended to the 20-27 milligram dose.

Now, these response rates numerically are higher, but the confidence intervals are overlapping. We therefore pooled data across most of our patients. We excluded the renal impairment study. We pooled 476 patients, performed a multivariate analysis to look a predictor of response. And the most important feature was the dose of carfilzomib with an odds ratio of 2.3.

DR. WILSON: Okay?

DR. FOJO: Yes. Just, I guess if the FDA is right in its concern about toxicity, longer

duration may be higher doses, that would be an issue that --

DR. WILSON: Right.

DR. FOJO: -- remains unresolved.

DR. WILSON: Right. It's a little bit of a cart and horse here because the approval would be for beyond second-line therapy, so you have to look at it in the context. I think that's what the follow-up studies would do. I think the critical part that we have to look at now is, is there a worrisome toxicity signal from the data we have seen so far. And I think that everyone's most worried about cardiac because it was seen in the animal models, and there were some cardiac events in this trial, in these trials as well.

Dr. Sekeres?

DR. SEKERES: Thank you, Dr. Wilson. Tito and I must have had the same sandwich from the snack bar today because I had almost exactly the same questions. But I'm going to ask them from a slightly different angle.

So can you clarify again, what percentage of

patients who had previously been exposed to bortezomib were purely intolerant; so not relapsed, not refractory, intolerant?

DR. LOVE: Yes, we can. Dr. Klencke?

DR. KLENCKE: It was 16 percent. And if I could have this slide up? I don't have purely intolerant on here. And, unfortunately, the numbers overlap considerably, but it was 16 percent that were purely intolerant.

DR. SEKERES: And I'm going to ask again kind of what you did. If you subtract out those 16 percent from your data, purely from this study, what is the response rate?

DR. KLENCKE: The closest thing I have -- if I could show -- there is a forest plot that shows bortez refractory, and another group bortez sensitive. The bortez refractory number was approximately 16 percent response rate, and the bortez sensitive -- yes, let's have this slide up. So in the middle of this slide, the bortez-sensitive patients did have a response rate of 40 percent.

DR. SEKERES: But that's not what I'm asking.

DR. KLENCKE: I know. And I don't have that --

DR. SEKERES: But please don't show slides when we're not asking that question.

DR. KLENCKE: Okay.

DR. SEKERES: Thank you.

So a question then would be, were the intolerant people lumped into the refractory population, or no?

DR. LOVE: No. The refractory analyses that you've seen are purely refractory. We did also show some analyses where we were looking at the combination. What we don't have in a slide is just intolerant.

DR. SEKERES: So I wonder then if a question for the FDA would be does that have to somehow make it into the label. This isn't really a relapsed/refractory population with respect to bortezomib; it's also an intolerant population.

DR. PAZDUR: We could discuss the labeling

with the company and get those numbers from them. But I think the point here -- we looked at this many ways, and we had a pretty consistent response rate.

DR. SEKERES: Okay. So my next question, you had said that patients initiated their response about 1.9 months following -- the median was 1.9 months, right? So when they started, the response then had to be confirmed 4 weeks later. So it begs the question that patients who've been exposed to bortezomib in the past -- do you have the range of exposures to bortezomib? So how many cycles?

DR. LOVE: So let me make sure I understand the question. We're looking for the range of exposure to carfilzomib, based on prior --

DR. SEKERES: No. So all of these patients had to have been exposed to bortezomib by definition to get onto this study.

DR. LOVE: Correct.

DR. SEKERES: Do you have the range of duration of exposure to bortezomib for this

population?

DR. LOVE: No, we do not. We only have data on the number of regimens, and the average person received two prior regimens of bortezomib.

DR. SEKERES: But if you have an average, then you should have a range or some sort of distribution around that average? What's your distribution around that?

DR. LOVE: So the number that I gave you was actually the number of regimens. It wasn't a number around the range of exposure that patients have had.

DR. SEKERES: So the reason I'm getting to this is that when we're dealing with a relapsed or refractory population for any cancer indication, part of our job is to figure out if they were truly relapsed or refractory, or they just hadn't received enough of an exposure to a previous medication. And this would be particularly salient with another proteasome inhibitor.

So you have no data about duration of previous exposure to bortezomib?

DR. LOVE: No. We focused on collecting data around refractory status, and most of the patients, as you've seen already, were actually refractory to bortezomib and refractory to lenalidomide.

DR. SEKERES: So the answer's no. You don't have a duration. You don't know if patients were exposed to bortezomib for 2 weeks or for 2 years.

DR. LOVE: We do not know that.

DR. SEKERES: Okay. Final question. What is the typical response rate to rechallenge with bortezomib? I'm not talking about worst-case scenarios. There's obviously a worst-case scenario. Are there any data that say, gee, if you treat somebody once with bortezomib, if you treat them again, be it a year later or 2 years later, this is their response rate?

DR. LOVE: I'd like Dr. Anderson to address that.

It sounds like Sagar will take it. They keep changing.

DR. LONIAL: Yes. Thanks.

DR. SEKERES: Is this elite status? Did I just get upgraded or downgraded?

(Laughter.)

DR. LONIAL: Well, Dr. Anderson would say downgraded. Sorry. And first, I didn't do my disclosures when I came up, so let me do that now. I'm an advisor to Onyx, but I'm not receiving compensation for my time here or in preparation for the meeting, but my travel expenses are covered.

So the question about retreatment with bortezomib, in the trials that were done looking at retreatment with bortezomib, they specifically picked out patients that had responded to bortezomib before, and the response rate is somewhere around 20 to 25 percent. So that's having received it before, sensitive, and then receiving it again.

Duration of response is slightly shorter than it was for the original exposure, and it varies based on how long they got it, whether it was induction therapy, salvage therapy, relapsed/refractory therapy. So I hope that

addresses --

DR. SEKERES: It's actually spot-on.

Now, could I ask the company one more time to put up that slide of patients who were relapsed from bortezomib? So previous responders and their likelihood of responding to carfilzomib.

DR. LOVE: The odds ratio plot? The forest plots, yes.

DR. SEKERES: So I'm actually looking for a response rate. So among patients who were treated with bortezomib in the past, which is all of your patients, patients who responded to bortezomib in the past and not the refractory population, what was the likelihood of them responding to carfilzomib?

DR. LOVE: Dr. Klencke?

DR. KLENCKE: Could have this slide up? In the middle of the slide, we see, "Bortez refractory in any prior regimen, yes or no?" "Yes, prior bortez refractory. Sixteen percent response rate? No, i.e., sensitive, 40 percent."

DR. SEKERES: Okay. Thank you very much.

DR. WILSON: I actually have a follow-on question, just in terms of how the myeloma community decides when to stop a drug. And maybe I can use my seniority and ask for Dr. Anderson to address this. But when you start a drug like bortezomib, and you only have a stable disease, would it be standard, like we do in lymphoma, to continue that drug until there was disease progression? This really gets at I think Dr. Sekeres' question about really how thoroughly were these patients really refractory, and what is kind of the median time to response to bortezomib in myeloma? These would kind of be similar, related questions.

DR. ANDERSON: So we'll just have a senior discussion between you and me, okay? But I do think it's a very prescient point. We do use treatment in protocols -- a defined number of cycles, et cetera -- to get drugs approved. But in terms of practice, we persist with active therapy, especially in this context, relapsed or relapsed/refractory myeloma, until progressive

disease.

DR. WILSON: And within standard practice, how long -- is it somewhere in the vicinity of 1 to 2 months before you see your response? I think that's what you typically see.

DR. ANDERSON: Yes. I think it's fair to say that it would be FDA-approved drugs and others for relapsed or relapsed/refractory myeloma. You usually see a response within the first month. Certainly, Wyndham, if you haven't seen a response in 2 months, you probably won't.

DR. WILSON: All right. Thank you. Nice to have a senior moment.

(Laughter.)

DR. WILSON: Dr. Buzdar?

DR. BUZDAR: Yes. I have one question. Looking at the data, there is no question that how the data is looked at, about 1 in 4 or 1 in 5 patients are getting clinical benefit or response. And there is about 7 to 8 months in the time to disease progression. The question is, is it having an impact on survival? Is there any hint?

If we look at the outcome from the time of diagnosis of the disease in this patient population compared to the previous experience -- I realize that this is a single-arm study, but looking at the natural history, the question is are we pushing the patient population and giving all those therapies in a very compressed format without having the clear maximum benefit from therapy, or is this a real gain, that you are controlling the disease for a longer period of time, which will, in the end, translate into a longer survival?

DR. WILSON: So maybe you can summarize it into a question for the sponsor?

DR. BUZDAR: The question is, have they looked at it from the experience from the previous studies, if you measure the survival from diagnosis of the patient population in this phase 2 study compared to the previous plots they had shown in the beginning?

DR. LOVE: The answer is no. We focused on identifying patients that were refractory and obviously relapsed. And that was really the

intent. I think that's the design that has been accepted as the way to try to identify patients where ORR should be predictive -- or may be predictive of clinical benefit.

DR. WILSON: Dr. Freedman?

DR. FREEDMAN: Thank you. This is just a question to get some clarification on phase 2 trials and their usefulness, particularly the results of those trials, putting them into labeling. I understand it's a difficulty there of getting accurate attribution information on the label. But here you've got another study, 009 -- we didn't hear much about it -- but could that study provide toxicity information that could be added to the label, if the drug was approved by accelerated route?

DR. PAZDUR: Well, a lot of that has to do with the timing of that trial and when it would be complete and data would be released. Remember, it's an ongoing trial, so we can't break the sanctity of that trial to put it in labeling -- that's for sure -- because it's an

ongoing trial.

Here again, the comments that are being brought up, we've discussed these multiple times in this committee, and they're just the shortcomings of the single-arm trial. One of the things that we had confidence in is this was quite similar to -- the response rate that's being presented here is quite similar to what we saw with bortezomib. In fact, it's in a more refractory disease population. And here again, bortezomib went on in confirmatory trials to show clinical benefit.

Unlike other single-arm trials that came to us, we already have a completed, basically, completely enrolled randomized study here, so it gives us a lot of confidence in this. And we could ask the committee, informally perhaps, even about the toxicity before approving the drug.

DR. WILSON: Dr. Neaton?

DR. NEATON: I just want to raise one other issue about the definition of response. And these are laboratory measurements that I know nothing about, and I respect the fact the committee's been

looking at this for a while. So in addition to the issue that this is a laboratory surrogate largely, you have an uncontrolled study, and people are being selected for progressing at entry. And so as a consequence of day-to-day variability in these laboratory measurements, you're going to see some regression toward the mean.

Now, I don't know how much regression toward the mean you would expect to see, but you would expect some number, some fraction of people, if there's reasonable variability in these measurements, to go from being progressors to being partial or, something, responders, even if you did nothing, if you just measured the data again. And I don't have any sense for that, based on -- and that's just a general problem with using a laboratory marker in an uncontrolled study, where you're selecting on the marker. And that's what I understand they're doing.

DR. PAZDUR: One of the reasons why we use response rate in all of these single-arm trials, whether it be in solid tumor, or in myeloma, or in

lymphomas, is that you would not expect a response to occur spontaneously. The degree of improvement that one would get a partial response or a complete response would not be observed by the natural history of the disease, so to speak. So that's why we're allowed to use a response rate in these diseases.

One does not see a 50 percent reduction by dimensional tumor measurements, or the response rates, as listed here, just by the natural history of the disease. That's why we do not, for example, look at survival times or time to progress in single-arm trials. Response rate is the only endpoint that we will look at in this disease setting.

DR. WILSON: So let me just get some clarification on that, Dr. Pazdur. I thought that FDA wanted that in conjunction with the duration, because a good response rate --

DR. PAZDUR: We always take a look at duration.

DR. WILSON: Right. I just want to clarify

that it's not just response rate. I think that if you have this response rate lasting one month, we wouldn't be here, quite honestly.

Dr. Fojo?

DR. FOJO: Since you brought that up, though, again, I think this is a different population than the bortezomib trial. I mean, these patients have made it 5 years. In fact, they're making it about 6 and a half years. So it's already a preselected population. It's a better biology, which comes to single-arm trials and whether you do historical control or whatever. So I'm sure you agree.

I just had two other questions. That's where Mikkael and I were trying to get at how do they -- you have here that those who -- you said there might be a bias of assigning progressive disease in patients who were progressing rapidly. And in support of the hypothesis, the hazard rate for progression or death within the first month after studying, it was 31 percent, compared with 11 and 16 in months 2 through 6. I would flip that

and say that's also evidence that those with the more aggressive disease, that are moving faster, are refractory to this disease, and those that are going to die sooner and progress sooner are actually doing just that. So it suggests that bad disease doesn't respond to this drug as well as one would like.

Do you follow what I'm saying?

DR. LOVE: I did not, actually. Could you reframe it? I did not follow it.

DR. FOJO: And I'm quoting from your thing.

DR. LOVE: Could you give the page?

DR. FOJO: Yes. It's on page 45 of 90, time-to-event analysis. PFS was performed on days 15 and 19. There may have been a bias toward premature assignment of progressive disease's best response since "these patients were actively progressing at the time of study entry."

In support of this hypothesis -- and remember here, by day 29, you were scoring a lot of people's MRs, so they've had plenty of time to respond. And on the one hand, you can't -- they

say, well, they didn't have enough time to respond. You can't have your cake and eat it too. So you say in support of this hypothesis that the hazard rate for progression or death within the first month after study entry was 31 percent, compared with 11 and 16 in months 2 through 6. And I would argue that that's evidence tucked in here that says that aggressive disease doesn't respond well to the drug, which would not be suprising.

DR. LOVE: I think there are more severe patients. I think at the end of the day, we are focused on the totality of the patient population, and we were not trying to make great claims around the time to event endpoints. We agree that those are limited interpretations.

DR. FOJO: Okay. And then the last question is, you talked about age and efficacy and less than 65 and more than 65, comparable. How about age and toxicity or tolerability?

DR. LOVE: Sure. Dr. Sacks?

DR. SACKS: Just to clarify, you're asking was there an imbalance or intoxicity profile

greater than or less than 65?

DR. FOJO: Correct.

DR. SACKS: Thank you. One moment.

(Pause.)

DR. SACKS: One moment. We do have that data. We'd like to obtain it for you.

It will take a moment to pull this data. Would we take another question and come back, or should we wait?

DR. WILSON: Maybe I will ask a question. I think that Dr. Fojo has been focusing on the fact that perhaps the natural history of this group is better than other studies. One of the things I noted was they took no primary refractory cases on this trial. If you look at the SUMMIT protocol for the accelerated approval of bortezomib, was that in fact the case?

I mean, I think you have what you've got here. I mean, you've got a group that they weren't primary refractory. They had 5 lines of therapy, and you got what you got. And I think you can talk about whether they're indolent or not, but the fact

is they didn't take any primary refractory cases. And this historical analysis here -- slide CM-9, on bortezomib, in the refractory myeloma, I suspect that did not focus on people that didn't have primary refractories; probably all-comers.

Maybe you could address that.

DR. LOVE: So you are correct, that we did not include primary refractory patients, and so we would expect our labeling to reflect that. With regard to the SUMMIT trial, Dr. Anderson can probably answer how that was conducted.

DR. ANDERSON: Yes, I'm very happy to. And the folks who conducted that trial from Millennium Takeda are here. And obviously, Rick Pazdur and Ann and others know it very well. But it did not allow primary refractory myeloma. That's a very good point because primary refractory myeloma is, as it says, refractory to its primary therapy but can clearly respond to other therapy.

So just as with the SUMMIT trials, so it is here, patients had to have relapsed myeloma, which then was refractory. And to Tito's point, this

actually came up exactly with the SUMMIT trial for bortezomib. And what we ended up doing -- because it wasn't clear that what you said isn't true; that you have selected outpatients with a different biology, who have more indolent disease.

So we actually went to a big analysis with the Mayo Clinic, as I'm remembering now, and we looked at what was the natural history of patients who had relapsed X number of times, because there were patients on the prior bortezomib trial who had relapsed 12 or 13 -- whatever. So the point was that the survival continuously decreased with increasing relapses.

Now, the slide I showed from ASCO, which was just a month ago or less -- the next one actually. No, that's not the last slide. But in any event, what it showed was that the response rates from -- here it is -- from 2007 to 2010, which I believe is the most recent data that I've seen available at least, shows up there that, in fact, the response rate does plummet with the relapses in a more current era. What we don't have right here

with us is what is the survival corresponding to those decreases, to your point. But if it reflects what was true previously, the survival that goes along with those response rates also shortens.

The biology here, I would tell you, is unfortunate because we start out with multiple abnormalities at the time of diagnosis, and then with each subsequent relapse, as we're now looking at more sophisticated genomic analyses, et cetera, is really complicated by more clonal abnormalities, more mutations, et cetera. So I think your point is well taken, but at least historically, we have not picked out the most indolent patients for the SUMMIT trial, and I don't think we have here either.

DR. LOVE: We'd like to come back to your 65 above and below question. Dr. Sacks.

DR. SACKS: Thank you. We submitted as part of the NDA a lengthy document, the Integrated Safety Summary. I do not have a slide, but I will describe to you the findings that were different with respect to safety terms for patients who are

above and below 65.

In the phase 2 population, it divided just about evenly between those below 65 and those above 65. And we searched for terms where there was at least a 5 percent difference in incidence. So in the older population, we saw a bit more thrombocytopenia and leukopenia. And, again, to be specific for leukopenia, when I make that statement, I'm referring to, say, an 11 percent rate in the younger patients and a 16 percent rate in the older patients.

The other events that came up in this analysis included fatigue, increased creatinine, and diarrhea, again, just looking for any event where there was a minimum of a 5 percent difference in reporting rate lower than 65 and greater than 65; so not an overwhelming signal of a different pattern, some events not expected, perhaps a little bit more myleosuppression, a little bit more fatigue.

DR. WILSON: Okay. Let me just ask the last question, and then we'll go ahead and have a break.

There's been some focus on cardiac toxicity. I think we've heard from the company that the relative incidence of cardiac toxicity is what you might expect in a population like this. But could you maybe give us -- and I realize that this is very conjectural, but could you at least let us know if there was anything from the animal models? I know there was cardiac toxicity in the animal models, but was the nature of it worrisome for something that might translate into humans, like the myofibrils were disintegrating or something like that?

But anyway, give us a little understanding about the pathobiology that you saw in the animal and also which animal, did you only see this in one animal model.

DR. LOVE: We'd be happy to. I'd like to ask Dr. Chris Kirk to address that.

DR. KIRK: My name is Chris Kirk. I'm the vice president of research at Onyx. Can I have the slide up, please?

We conducted our toxicity studies, both

acute and chronic, in rats and monkeys, the same species used to test it on clinical toxicity of bortezomib. In addition, we did some comparative studies, utilizing bortezomib and carfilzomib in the same study, in rats in the acute setting.

What I'm showing here are the major toxicologic findings, both acutely and chronically, in rats and monkeys. You'll note that for cardiovascular, pulmonary, GI, renal and hematologic, the findings between bortezomib and carfilzomib were essentially identical. In particular with cardiovascular, this was the dose-limiting toxicity for bortezomib in animal studies. It's important to note that the one major distinction between the two agents in animal studies was neurologic in the fact that there were no neurobehavioral or histologic changes to the peripheral nerve.

Can I have the next slide up, please? Specifically to cardiovascular toxicity, the death in animals due to cardiovascular toxicity occurred with both agents at doses lower than the human

equivalent dose in both rats and monkeys, but was remarkably similar between the two species. Cardiomyopathy, necrosis, fibrosis, hemorrhage and edema were the major findings. In monkeys, there's an acute hypotension with a concomitant tachycardia. However, when the drugs were administered at their maximum tolerated dose, 2 rats and monkeys -- and this is true for both agents -- only findings of sporadic cardiac inflammation were the major findings.

We took this information going into the phase 1 trials rather seriously and conducted the phase 1 studies with this information in mind, but also understood that given the identical preclinical findings of bortezomib and its clinical safety profile, we have some comfort.

DR. WILSON: Okay. Thank you. I think with that, let's go ahead and adjourn for break. We will reconvene at exactly 3:30. And please, members do not discuss this among yourselves. Thank you.

(Whereupon, a recess was taken.)

Open Public Hearing

DR. WILSON: Okay. We're now going to be entering the open public hearing.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial

relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way, where each participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

We welcome each speaker, and there will be a clock there. And at the end of your time, the light will turn red, and the microphone will be turned off.

So with that, I invite speaker number 1.

MS. AGARWAL: Good afternoon. I'm Veena Agarwal. I'm grateful and fortunate to share my experience with carfilzomib at this advisory committee meeting. Onyx Pharmaceuticals is gracious enough to provide me with hotel accommodations and other facilities.

Currently, I'm in ongoing treatment with multiple myeloma. I was diagnosed with myeloma in November 2007. I received my bone marrow transplant in June 2008. I was in complete remission for only two months, and this was very, very disappointing. The next treatment that I was put on was with Revlimid, but I was never in remission. With the Revlimid treatment, I started to experience neuropathy. At this point, Dr. Jaggernauth and Dr. Chari (ph) discussed carfilzomib with me, and my treatment with carfilzomib started in October 2009.

The immediate response was that my numbers started going down. I was near complete remission by the 9th cycle, and carfilzomib kept my numbers in check until 19 cycles. I took a three-week

vacation to India, and during that time, I could not take carfilzomib. On my return, my numbers have gone up and they've stayed up, so cytotoxin was added to my treatment. I received 27 mg dose of carfilzomib twice a week, with three weeks on and one week off. I still experienced neuropathy.

On the chemo days, I was light-headed and sleeplessness, with occasional back spasms and nausea. My stamina has gradually decreased, but I can still go for walks for 30 to 45 minutes daily. I'm an artist, and I'm able to continue to sketch and paint. I'm grateful for having the benefit of receiving carfilzomib treatment today, and it is my hope that other patients are also so privileged. I don't know what the future holds, but I think it is important for others to have the options of treatment like this now, while still they can.

I'm approaching my fifth year with multiple myeloma. My treatment has helped me live my life with my family and friends. I'm not afraid of multiple myeloma, and I can do things with the people I love. I can laugh, I can sing, and be

happy. Thanks to carfilzomib for prolonging my life. Thank you.

DR. WILSON: Thank you very much. Speaker number 2.

MS. TUOHY: My name is Robin Tuohy. I have no disclosures. I am a caregiver to my husband Michael, whom you will hear from momentarily. Michael was diagnosed with multiple myeloma more than 12 years ago in August of 2000. I am also the director of support groups for the International Myeloma Foundation, assisting more than 100 myeloma support groups across the United States. Wearing both hats gives me a unique perspective on the urgency of having another cancer drug patients can turn to in order to save their lives.

I speak as a loving wife, and also I speak for the thousands of patients and caregivers who are represented and supported by the International Myeloma Foundation. Thanks to new drug treatments, my husband has not only survived well beyond the life expectancy we were quoted at his diagnosis; Michael has thrived. He has seen our daughter

Ally (ph) complete her freshman year of college and our son Mikey graduate eighth grade just last night. But like all others who are living with myeloma, we are guaranteed two things. One, the disease will return. If a patient is one of the lucky ones who live long enough, it will return time and time again. Two, the treatment that worked miracles before will become completely ineffective. Each time myeloma returns, it is progressively more and more difficult to fight back with existing therapies.

For these reasons, the availability of a new cancer drug like carfilzomib literally means life for myeloma patients who have run out of effective drugs in the disease-fighting arsenal. No new drugs have been approved for multiple myeloma in nearly six years. A new drug such as carfilzomib would fill the void when patients have stopped responding to available treatments. Myeloma patients like my husband Michael, and the tens of thousands of others across the United States, are waiting for you to help save their lives. Some of

them cannot wait any longer. Our friend Jeff has given me permission to share his story.

Jeff was in his early 40s when he was diagnosed with myeloma on New Year's Day 2004. His disease is very aggressive. Jeff has tried every treatment option available and is currently on a clinical trial with carfilzomib. It is saving his life. However, due to this treatment -- access to this treatment comes with a high price. He needs to live near a myeloma center for nine months out of the year. This center is thousands of miles from his home. His wife continues to work and is only able to visit him a few times. Mentally, financially, emotionally, this has drained them. Access to this life-saving drug is imperative for Jeff and all replased/refractory patients today.

As a caregiver, I know, as well as my husband Michael, that each drug has side effects, and patients have to weigh the risk-benefit ratio. But it's our lives, and the choice is always to take the risk and to live. The longer we live, the closer we will be to a cure.

Thank you for giving me this opportunity to lend my voice to the support for the approval of carfilzomib.

DR. WILSON: Thank you very much. Speaker number 3.

(No response.)

DR. WILSON: Speaker number 4.

MR. TUOHY: Good afternoon. I'm Michael Tuohy. I have no disclosures.

My name is Michael Tuohy. I am a myeloma survivor. I was diagnosed with multiple myeloma when I was 36 years old in August of 2000. My children at the time were 2 and 7 years old. Needless to say, my wife Robin and I were devastated. Life expectancy in 2000 ranged between 18 months and maybe 5 years. That was not good enough. I was afraid my children would not even remember me.

Thanks to research by many of you here today, there are more options available to patients, and we are living longer with a better quality of life. Continued research and approval

of drugs is imperative so that patients can have access to them and are able to live to see the next drug approved. We live from treatment to treatment to treatment, and the options we need to continue so we can be here for the cure.

In 2000, options were extremely limited, and we lived with a heavy burden of trying to keep something in our back pocket, a big gun for when you really needed it. Today, we are able to treat myeloma in sequence and in combination. There is much more hope in our futures. Each new drug approval extends our lives. There is no cure to date for myeloma, so now we live from drug to drug. In the relapsed/refractory setting, when the disease comes back, it is always more aggressive. The drugs needed to combat myeloma in this setting are key and must be available to patients.

I wanted to be here to watch our children grow up and to be here for my wife. The more options we have, the greater the chance I have of living a longer life. A stem cell transplant brought me a three-year remission before I

relapsed. Fortunately at the time, there was another drug and clinical trials which I was able to access. I've been on this drug for seven years and in complete remission. I wish this for all patients out there that are in this position.

Side effects don't scare me. I can deal with them. All drugs have side effects, and we need to weigh the risk-benefit ratio. The alternative, quite frankly, is death. I choose life, and I hope you do, too, and recommend carfilzomib to the FDA for approval. Thank you.

DR. WILSON: Thank you very much. Speaker number 5.

MR. RICKERT: Good afternoon, and thank you very much for giving me this opportunity to speak to you all about my carfilzomib experience. Before I get started, I want you to know that my time is purely voluntary, and Onyx has offered to reimburse my travel expenses.

Now that I've got the housekeeping out of the way, my name is Doug Rickert. I'm 57 years old, live in Wyckoff, New Jersey with my wife and

three school-aged kids. Professionally for the last 10 years, while undergoing treatment for myeloma, I've run two small companies and provided consulting services to others. As background, I was diagnosed in November of 2001. Since then, I've received six lines of therapy, including radiation, thalidomide with dexamethasone, cytoxin, melphalan, an autologous stem cell transplant, thalidomide with dexamethasone, and Revlimid with dexamethasone, and now carfilzomib with dexamethasone.

For those of you that are concerned about the gaps in treatment, I had 18 months after my transplant where I was remission-free and didn't take any therapy and also 25 months after Revlimid. The doctors and nurses and the staff at the John Theurer Cancer Center in Hackensack University Medical Center provided guidance. They held my hand through each of those therapies.

Just about three years ago, I had a choice: Revlimid, Velcade or carfilzomib. Dr. Siegel, who I believe may be here today, laid out the pros and

cons of each therapy, and I chose the latter. I found it to be safe, reliable and effective at slowing the growth of my cancer. I've been on a biweekly therapy since December of 2010 and actually thought about walking away many times for another remission gap. But since my response to carfilzomib was and is so good, I decided to stay on to become a statistic and hopefully improve its chances of gaining FDA approval. I guess I'm a little more than a statistic now.

My treatment decisions were not just for long-term effectiveness, but for the time requirement, the administration methods, and most of all, the short-term side effects. During all of the therapies, I developed peripheral neuropathy, irritability, and fatigue, and as an aging athlete, the healing process of cuts and bruises seemed to take forever. In contrast, while taking carfilzomib, my neuropathy lessened. I can wear flip-flops again. You know, I can walk on the beach with my wife. My temperament seems to be a little bit more even-keeled My energy level is

back to what I remember it to be, and the healing time has improved significantly.

Yesterday, I completed my 20th cycle, drove 250 miles to attend this meeting, went to Blacks and watched LeBron's Heat take a commanding lead in the NBA finals, before retiring last night. When I leave tomorrow, I'm driving to Boston to watch the Boston/Marlins' game and my daughter play a lacrosse game. Does that sound like a person that's at risk for taking carfilzomib? I think not.

In closing, as you can see, I live in the fast lane, and carfilzomib has significantly improved the quality of my life. Please approve this drug. Thanks for your time.

DR. WILSON: Thank you very much. Speaker number 6.

MS. MORAN: I have no disclosures. My name is Diane Moran. I'm the senior vice president for strategic planning at the International Myeloma Foundation. I'm an experienced nurse with advanced degrees in education, and I have two decades of

experience working within the pharmaceutical industry before coming to the IMF. We're the oldest and largest myeloma organization, serving the myeloma community for 21 years, so we speak to you with experience.

At the IMF, one of my areas of responsibility is our nurse leadership board. They work directly with the patients and their families, and they are intimately involved with the patients' personal and medical needs and concerns. Given my own background and what I've learned from working with the nurse leadership board, I also speak from a hands-on point of view.

From these perspectives, the most important message I can impart today is that patients must have continous access to new drugs that will keep them in remission until we can find a cure. They know there are risks. They know nothing's perfect. But above all, what they know is that dying from myeloma is just not an option.

Over the past decade, tremendous strides have been made in treating myeloma. The experts

assesmbled here today will agree that myeloma outcomes have dramatically improved. Myeloma now can be managed with the use of drugs in combinations and sequence to build long-term remissions back to back, but a string of remissions is just not a cure.

In 2009, the International Myeloma Working Group, the scientific arm of the IMF, undertook a study of patients who had relapsed or refractory to one of the IMiDs as well as bortezomib, a total of 300 cases: 8 sites in the U.S., 5 in Europe, 1 in Asia. The lead author, Dr. Saji Kumar from the Mayo Clinic reported their findings in the Journal of Leukemia. And I quote, "Our results confirm the poor outcome of patients once they become relapsed and refractory to agents that have become the mainstay of myeloma therapy. The findings highlight the incurable nature of the disease and urgent needs to develop newer, effective, therapeutic agents for this group of patients who currently do not have effective treatment options." Without a new treatment, their overall survival was

a median of 6 months. Event-free survival was 1 or 2 months, which means their condition deteriorated right away.

Carfilzomib is a crucial option for these patients. Terminal patients do not have a second chance if other options are not available. There are always potential risks with new treatments. Time is precious. Life is precious. Myeloma patients need access to every new therapy. They need and want the opportunity to consider the risks and benefits on an individual basis. Access to new drugs such as carfilzomib is essential to provide hope, and most importantly, a real opportunity for survival. How could anyone possibly deny patients that right?

I want to thank you for this opportunity to speak to you on behalf of the International Myeloma Foundation, and more importantly, the myeloma patients we represent.

DR. WILSON: Thank you. Speaker number 7.

DR. BARRAGER: Good afternoon. I want to thank Onyx for covering travel so I can testify

here, and I appreciate your kind attention.

Two and a half years ago, I was in a desperate situation. My multiple myeloma was raging out of control. During the previous three years, I've been treated with Velcade and then Revlimid. One lowered my IGA counts but destroyed my quality of life. The other was more friendly in terms of side effects, but couldn't control the cancer. A stem cell transplant was not an option for me. I believed I was at the end of my rope.

As a last effort, my oncologist told me to look into a carfilzomib trial. When I was accepted in the trial, my IGA was so high that if the drug failed to work, I was a goner. The great news is, after only three months, my multiple myeloma was back down from an IGA of over 3600 to about 200. After two and a half years of carfilzomib treatment, I am living a productive life again. My doctors are optimistic about the future.

I want to urge the FDA to approve carfilzomib immediately for use by patients with relapsed and refractory multiple myeloma. I'm a

70-year-old grandfather. I've spent my professional career as an engineer, entrepreneur and professor. In February 2007 doctors discovered that I had stage 4 acute multiple myeloma. At the time of the diagnosis, my kidneys were failing, seven vertebrae had collapsed. I was weak and in severe pain. My IGA counts were about 1900.

Initially, I was treated with a combination of Velcade and dex. The high doses of dex made me agitated and socially difficult. Though Velcade was able to lower my IGA into the normal range, my quality of life was terrible. I quickly developed severe neuropathy in my feet. The pain was so bad, I could not walk one short block from my home to my office. After Velcade, I was switched to Revlimid.

To shorten my talk, we need an alternative treatment, and there are none for people in my situation, or there were none. Thanks to carfilzomib, I've been able to resume an almost normal, productive life. My physical strength is returning. Recently, I had the energy to launch a new company. I urge you to approve carfilzomib.

Thank you.

DR. WILSON: Thank you very much. Speaker number 8.

MR. CAPONE: Good afternoon. My name is Walter Capone with the Multiple Myeloma Research Foundation, and I have no disclosures. I'd like to thank the distinguished members of the ODAC and the FDA for the opportunity to address you regarding the carfilzomib NDA, on behalf of our foundation and the thousands of patients, their families and friends, as well as the clinicians and researchers with whom we work each day.

Myeloma remains an intractable and fatal blood cancer, with a five-year median survival rate of just 38 percent, one of the lowest of any cancers. For refractory patients, like those being considered in today's meeting, the median survival, as you've heard, is a matter of months, less than 10, perhaps 6 at best, and standard cytotoxic therapy is essentially palliative if it can even be given at all. Such patients comprise the majority of nearly 10,000 to 11,000 who die each year of

myeloma and desperately need new active options. Carfilzomib has shown the potential to extend life in such patients with survival well over a year, providing tremendous benefits and hope to them, their families, and their communities.

In our experience with carfilzomib since 2006, in working with hundreds of patients at the MMRF and our collaborators at the MMRC, we have seen meaningful benefit become a reality for many, with quality and length of life significantly improved. Most recently, over the last nine months, in facilitating C-MAP, the carfilzomib expanded access program for refractory myeloma, the rapid attainment of full enrollment within three months of initiation reflects the urgent need for new active drugs, and Onyx has responded accordingly by doubling the size of the study to over 500 patients, 500 patients who would otherwise not have access to carfilzomib and its potential for benefit and hope.

Furthermore, as a patient community, we, like you, also see an incredible and rare

opportunity, where over the next six months, the potential exists for not just one but two novel active drugs potentially to be approved for refractory myeloma patients. Such patients will finally have the chance to reset the clock to when they first began myeloma therapy by combining two new active drugs that together could enable a profound and prolonged remission. Short of a cure, this is what all patients aspire for, demand, and deserve.

Considering the comprehensive phase 3 program currently in progress and numerous late-stage development studies, both planned and ongoing for carfilzomib, Onyx's commitment to the myeloma field is clear and should provide confidence to the committee in favoring the conditional approval of this agent. In doing so, the committee could also potentially set the stage for multiple new active drugs available this year and transform the lives of thousands of patients, as Dr. Lonial mentioned earlier, who might otherwise die while waiting for full approval.

In closing, I want to thank you all for your service on behalf of patients and their families and reflect on them for a moment. Three courageous friends, George, Laura and Bill, sadly have run out of options and died in the last two weeks. For all refractory patients still with us, we implore you to act favorably regarding carfilzomib and confer potential benefit, and help the patients today. Thank you very much.

DR. WILSON: Thank you very much. Speaker number 9.

MS. WOLVERTON: Thank you very much. My name is Amy Wolverton, and I appreciate the opportunity to speak with you all here today. I have no disclosures.

I was diagnosed with myeloma in my 30s, and at that time, the first two doctors that I spoke with basically said, "Get your affairs in order." And that didn't set well with me, so I kept pressing on for other options and solutions, and I finally found a clinical trial to participate in. But, unfortunately, that didn't work out so well.

It was a trial with transplant, and my stability of disease only lasted about two months. So I had to find yet another doctor and more care to get on Revlimid, which had held me stable for a couple of years. But now, unfortunately, I'm in the position of needing something else. My disease is already progressing again.

We've tried several treatment adjustments in the last six months, but those haven't worked yet for me. And while I'm particularly young for myeloma, there are more and more patients like me who are being diagnosed at a younger age. And because myeloma is incurable, many patients like me particularly hope that we can make this a chronic condition, where we can almost make it like diabetes, where you can manage it with medication. But as you all know, the drugs don't work indefinitely, and so we need to be able to go from drug to drug to drug and have different options. Not every medication works for every patient, so the more options that are out there, the better.

Also, many of the treatments are only

working for months, which, as a patient, those months are critical. But it's just all the more reason that we need more options. I understand the rates that were talked about today were 22 percent response rates with carfilzomib, but that's 22 percent of myeloma patients who might have an option, who might have additional months to their lives than they would without this drug.

I do understand the side effects and risks, as you've heard from other patients here today. And I tell you what; if my choice was letting the cancer get the best of me or take on some side effects or risks, I'd take on those side effects or risks. And I would ask you all to think about if you had family members, if your parents, your siblings, your children had myeloma, wouldn't they want to take on those risks, probably, and have months, maybe years, and a lot of hope added to their lives?

Again, I want to thank you very much for your time today, and I urge you to approve this medication.

DR. WILSON: Thank you very much. Speaker number 10.

MR. WESTRICK: My name is Paul Westrick. I'm a 15-year myeloma survivor from Milwaukee, Wisconsin. I have no financial disclosures. I appreciate this opportunity to provide a brief testimonial concerning a product that's making a very positive difference in my life. I realize that, like each of the individual myeloma patients that have presented this afternoon, I represent an anecdotal sample of one.

As oncologists, researchers and statisticians, you must deal with both the scientific evidence and patients at the aggregate level. But as patients, we hope for the best in our individual experiences and treatment outcomes. We hope to beat better the depressing odds and statistical evidence captured as response rates and duration to relapse or death that were shared earlier.

The advent of targeted therapies, like carfilzomib and combinations of these emerging

drugs, are pushing more of us toward increased quality and expanded quantity of life. My goals have always been to outlive those median group experiences, and I've been fortunate to reset new benchmarks every several years, seeing my children graduate from high school, then from college, and now the next horizon, hoping that they'll eventually leave the nest.

As a 15-year survivor, I've been relatively fortunate in my experiences with myeloma. This time has been marked by periods of watch and wait, punctuated by an autologous stem cell transplant in 2003 and a recent relapse. Upon relapse, I sought what I felt was the most effective and appropriate treatment option available. I'm currently in active treatment at the Medical College of Wisconsin in Milwaukee, participating in the ASPIRE phase 3 trial, with the same carfilzomib dosing that was shared earlier, with a combination of Revlimid and low-dose dexamethasone.

Today actually marks the completion of my sixth cycle, and I've achieved a near-complete

response, based on recent results. These measured results exceed those of my autologous transplant, during which I was out of commission for over two months. With this treatment, I haven't missed a beat on the current regimen. Over the past six months, I've been able to maintain an over-subcribed lifestyle as husband, father, health system executive, active board member for leukemia and lymphoma, and a variety of other roles.

While I'm not part of the study group under consideration today, I feel that I do represent the broader multiple myeloma patient population. People can benefit significantly from access to this drug. On that basis, I ask that you consider approval for the application. Thank you.

DR. WILSON: Thank you very much. Speaker number 11.

MS. MULLIN: Good afternoon. My name is Libby Mullin, and I'm here on behalf of the Cancer Support Community. It's an international, nonprofit organization, that provides support, education and hope for people, family givers,

caregivers, and the patients affected by cancer. For the record, the Cancer Support Community does receive funding from Onyx, however, we received no funding or compensation for our presence here today.

The Cancer Support Community offers free programs, including professionally led support groups, educational seminars, nutritional workshops, exercise and, mind/body programs to caregivers, patients, and their loved ones. Our mission is to help people living with cancer regain a sense of control over their lives, feel less isolated, and restore their sense of hope for the future, regardless of the stage of their disease. Last year, we provided support services to more than 300,000 people with cancer, including those living with multiple myeloma.

At the Cancer Support Community, we have learned a great deal from those we support, and we believe in the importance and value of an educated an empowered patient. Since people living with cancer often feel stigmatized, alone, and

overwhelmed with grief, they feel stronger and more hopeful when they have more treatment options available to them.

With an estimated 21,700 new diagnoses of multiple myeloma in 2012 in the United States alone, we are in great need of improved treatment options and better access to those treatments, especially when a treatment promises improved survival outcomes, manageable side effects, and other positive outcomees. This is particularly important for people dealing with multiple myeloma who have limited treatment options. We have the opportunity to expand the chances that these families have a better life with new treatment options and feel strongly about supporting that opportunity.

Today I ask you carefully to consider the plight of people dealing with multiple myeloma and understand the range of both physiological and psychosocial issues that they face. Please take a leadership role in improving the broader range of options and encourage patients to be informed,

empowered and optimistic about the possibility of a longer, healthier life. Thank you.

DR. WILSON: Thank you very much. Speaker number 3.

(No response.)

Questions to the Committee and Discussion

DR. WILSON: This concludes the opening public hearing portion, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments. We will now proceed to the questions to the committee. If FDA would like to present it?

DR. HERNDON: Given the following, a response rate for the primary efficacy study of 22.9 percent, a median duration of response of 7.8 months, life-threatening adverse events seen at low frequency in single-arm trials among heavily pretreated patients, the question for the ODAC is, has a favorable benefit-risk profile been shown for the treatment of patients with relapsed or

refractory multiple myeloma who have received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent?

DR. WILSON: Okay. Thank you.

Members, if you have comments, please raise your hands? Let me just say that I think we heard the evidence presented here. The sponsor has presented a clinical trial, which has shown a 22.9 percent response rate in patients who are either refractory to or intolerant of standard therapies, including the two most recently approved drug, the IMiDs and bortezomib. One of the questions at hand is whether or not the benefit is offset by the risk. We see that the median duration of response is in fact approximately 7.8 months. We've also seen that there is cardiac toxicity. Cardiac toxicity was seen in animal models. The nature of it within the animal models appears to be similar between carfilzomib and bortezomib.

I am of course very concerned with any life-threatening toxicity, however, having treated

many highly refractory patients, the level of cardiac toxicity does not appear to be out of proportion to what you would normally see. And in fact, the company did present evidence that the frequency of cardiac toxicity in a population like this is very similar to that which they saw, which is in the 5 percent range.

So I think the question before us is whether or not this agent has demonstrated the likelihood of showing clinical benefit in a population in whom there is no available therapy. And so with that, let me call on Dr. Omel.

DR. OMEL: Thank you. Myeloma is a really sneaky disease. You get an effect for a while, and then the pathway that's being blocked no longer works. We have to add a second drug to block escape pathways. We need new drugs constantly because this cancer is just absolutely difficult to control, totally incurable. The clinicians, Dr. Anderson, Sagar, they need all of the different treatment options that they can to block the various pathways of escape that myeloma takes.

A comment on this trial about preselection of better patients. Overall, 85 percent of myeloma is standard risk; 15 percent of us are at high risk. In this particular trial, 28 percent of the patients had poor cytogenetics, so there really wasn't any preselection of better patients. And the fact that they had lived five years is just the nature of changing myeloma treatment.

We have good treatments now, thanks to the FDA and the various drug companies. They last. We get five years. Mike at 12 years, and me at 15 years, Paul at 15 years, we are the exception, thank goodness, going forward. It will probably and is getting better, but we all run out of treatment, treatment options. We relapse. The biggest risk when it comes to myeloma is the risk of dying before we get to our next treatment.

As all of the speakers said, and I would certainly attest, we will all accept the risk of cardiac, liver, pulmonary toxicities before we'll accept a sure, 100 percent risk of myeloma. We know what the risk of myeloma is, and it's a heck

of a lot more than the risk of this particular disease.

I also would ask the committee to think about who is at risk. Sure there's a risk, but the risk is for myeloma patients who really don't have the other options. We have shown that we will gladly accept the risk of secondary cancers by taking Revlimid maintenance. I've done that myself. I have no qualms about the secondary cancers. I would have no qualms about carfilzomib's risk. And I sit on the panel, basically representing thousands of myeloma patients who can't speak to you as I am privileged to do.

The thing about carfilzomib, if it doesn't cure our myeloma, it won't, but it will buy us time. It will buy us precious time until we can get closer to a cure or until we can get to the point where another drug, pomalidomide, whatever, comes on. We just want to stay alive, and carfilzomib has given 22 percent of these patients, who's never -- you know, they had no other options.

They've run out of their choices. It gives them the time. Thanks.

DR. WILSON: One of the issues I think that we need to consider whenever thinking about accelerated approval is the status of the confirmatory trials. And it's already been mentioned, but I think it's worthwhile mentioning that at a previous ODAC, a number of issues came forward.

First, most ODAC members recommended that even for accelerated approval, that a randomized study be done. However, I think that we all recognize that there are settings in which single-arm trials can be done if, in fact, it is done in a setting in which there is no other standard therapy, and I think that's the case here.

The other recommendation was that confirmatory trials be planned and ideally underway at the time that accelerated approval was granted by FDA. And in the current case, the confirmatory trial, which is being done under a SPA, actually, not only is it underway but it's actually completed

enrollment. And another confirmatory trial for a new indication has yet to begin enrollment. But we do have one large confirmatory trial that has completed enrollment. So I do think that from the recommendations that came out of the ODAC around 6 to 9 months ago, that the current submission does fulfill some of the basic endpoints or timeline issues that were recommended.

Does anyone else have any other comments? Dr. Fojo?

DR. FOJO: Can I just ask the FDA two questions?

Dr. Pazdur, you did say response rate was enough in this setting; don't have to worry about the duration of response.

DR. PAZDUR: Yes. You want to make sure that these aren't just transient responses --

DR. FOJO: Right.

DR. PAZDUR: -- when they're brought out, but it's a time-to-event endpoint in a sense. We do take a look at the duration of response in an effort to make sure that these aren't just

transient responses, and I don't think anyone would call a response with a median duration of 7 months a transient, clinically meaningless response. So that is mainly to look at if the response was 25 percent and it lasted 2 months, or a month, or something like that, then I think people would have concern. That's not the situation here.

The other issue that you brought out, with the single-arm nature, is there always is patient selection. And anyone that has met these criteria, being refractory to multiple drugs, there is a patient selection here. The flip side of this is -- for some reassurance here for the members -- that when we have a population such as this, and we do see activity, it probably represents a drug that has a unique mechanism of action in a sense. And that's why I think we have been willing, as an agency, to take a look at these very refractory populations and approve drugs on these basis.

Yes, it is a selected population. Anybody even that goes into a phase 1 study probably is a

selected population because they've gotten there, so to speak. But here, with a response rate in this population that is very refractory, it probably represents a mechanism to find drugs with novel mechanisms of action. And that's another way of looking at it that we've discussed.

DR. FOJO: And then the other question I had, the document we had before the meeting, I mean, it conveyed greater concern I think with regard to toxicity than was conveyed here. The body language here didn't quite fit that document. Maybe Dr. Herndon wants to answer that. Is that a correct interpretation, that you feel not as -- or Dr. Farrell?

DR. FARRELL: I would say we don't have the same degree of concern.

DR. FOJO: Okay.

DR. WILSON: I think it's important that the ODAC should be considering the data that's presented and not the interpretation that is at the end of a document.

Yes, sir?

DR. NEATON: A comment, and then maybe a question for the FDA. Dr. Wilson, you've raised two questions. One you paraphrase this one, which I think is a very hard one to address in a single-arm study, balancing risk and benefit. And I think the sponsor acknowledged that today. You just simply don't have the control arm. But the other question you raised was the likelihood of showing clinical benefit. And certainly there's sufficient data here, I would think, that would warrant the conduct of the trial that they've done.

So I guess my question to the FDA is suppose this is approved on accelerated approval, and the phase 3 trial shows no difference? What are the consequences?

DR. PAZDUR: Well, as people know on this committee very, very well, from having lived an experience almost a year ago, we do have a mechanism to remove a drug that has received accelerated approval that fails to demonstrate clinical benefit. However, comma, there is a body of information that we would want. There are

ongoing trials here, not only one trial that we'll have. So it's not an either/or mechanism of, okay, you failed this trial, the drug comes off. I think what we're more interested in is taking a look at what is the body of evidence that is emerging on this drug.

For the breast cancer drug that was very topical, last year there was a body of five trials which really did not confirm clinical benefit, not just one trial here. But there is a mechanism to remove a drug. If the FDA feels that the body of evidence does not constitute clinical benefit, that drug can be removed.

DR. WILSON: I mean, I think that one of the things that Dr. Pazdur brought up is that -- and, actually, the reason why I asked this question early on is that this drug appears to have a mechanism of working that is somewhat different than bortezomib because in bortezomib refractory cases, it had a response rate of 18 percent. And that's bortezomib given in the most recent therapy. And that actually is a very compelling argument,

that this drug is actually adding something to a drug that's already out there.

I think the toxicity spectrum of this, for those of us that treat cancer patients, especially those that have had as much therapy as these have, really is not of major concern so far. Obviously, there's only limited experience with this, relatively speaking, but still it goes into the hundreds. And there is some long-term exposure among around 60 or 70 folks.

So I mean everything has to be put within context of the fact that this is an unmet need in a group that has really run out of options. And there is I think a pretty convincing signal here that is likely to, I believe, be confirmed in confirmatory trials. Obviously, I think my bias is coming through, but go ahead, Dr. Sekeres.

DR. SEKERES: Thank you, Dr. Wilson. I was hoping to ask a little bit of a provocative question to the FDA and possibly set the stage for a future meeting. I notice the potentially confirmatory study is under a SPA with an endpoint

of progression-free survival. Is PFS going to continue to be an acceptable endpoint in myeloma studies?

DR. PAZDUR: We have approved drugs and denote a clinical benefit on that basis, progression-free survival. So this would be consistent with past regulatory actions. Here again, I would like to put caveats around that. That is not just any progression-free survival. We take a look at the magnitude. We take a look at risk-benefit, what are the toxicities of these therapies, et cetera.

DR. SEKERES: I look forward to discussing in about a month.

DR. WILSON: Well, I mean, I think it's a real issue, especially if you're doing clinical trials where the drug is already on the market. That's really going to obscure the survival advantage if the control arm can get their hands on it. So I think it's simply the reality of the setting.

DR. FOJO: Is that more your bias coming

through?

DR. WILSON: No, it's not my bias. It's that if a drug -- if you're doing a confirmatory trial for an accelerated-approved drug, the drug's out there, and people who are on the control arm can get it. So it's not biased. It's just the facts of clinical trials.

Further questions? Any thoughts?

(No response.)

DR. WILSON: Okay. Well, with that, why don't we go ahead and move to the voting question. Before you, you will see that on your microphone, there's a "yes," "no" and "abstain" button. When we're ready to vote, that's going to light up. And the voting question is, is the risk-benefit assessment favorable for the use of carfilzomib in the treatment of patients with relapsed and refractory multiple myeloma who have received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent? A yes vote is, yes, it is favorable. A no vote is, no, it's not favorable. Please go ahead and vote.

(Vote taken.)

DR. WILSON: So the voting results are yes, 11; no, zero; abstain, 1. And so what we will do for the voting members is we will go around the room, and please state your name into the record, how you voted, and give a very brief reason for why you voted as you did.

So why don't I go ahead and start on the right side.

DR. NEATON: Jim Neaton. I abstained. This is not an area of my expertise. But I have to say I'm very nervous about the outcome as it was assessed in this study and kind of being able to reliably assess risk-benefit here. And so I abstained because of not being knowledgeable enough about the field.

DR. MENEFEE: Michael Menefee. I voted yes. I also was actually -- I'm nervous about this for some of the reasons that Dr. Neaton mentioned. However, I do think that this drug is beneficial to this patient population. And given the limited therapeutic options available and the mechanisms to

perhaps rescind the approval if safety issues persist in the future, led me to vote for approval.

DR. FOJO: Tito Fojo. I voted yes. I guess I would say that it has a benefit-risk profile that does not appear unfavorable, rather than it appears favorabale. And I respect Dr. Pazdur. I'm surprised he thinks it's a different drug. I was kind of disappointed we were really doing a me-too drug at some level, compared to Velcade. And so a better drug would have been more exciting, but it is what it is.

DR. BUZDAR: I voted for the drug based on I think 1 in 5 patients was getting benefit. And also, the safety profile in the heavily treated patient population was acceptable, because I treat breast cancer with a similar type of long, natural history. And when you treat these patients -- because these treatment side effects are cumulative, and these patients were 6 or 7 treatments previously, a number of them are potentially cardiotoxic. Then any additional insult to the myocardium or to the lungs can cause

limited results or become compromised.

So I think, overall, in spite of some of the concerns about the safety, overall, the safety profile looked to me acceptable, and, overall, the therapeutic index was favorable.

DR. WOZNIAK: Antoinette Wozniak. I voted yes. I think the drug has activity. As far as the safety profile goes, I'm encouraged by the completion of that phase 3 study.

DR. KELLY: Kevin Kelly. I also voted yes. This drug does have clinical activity and I think will translate into a clinical benefit. For the toxicity profile, I wasn't too concerned about that. But I was really more concerned about the phase 3 being completed and no real big signal that came out in phase 3. And I think that we have to take that into consideration, too.

DR. SEKERES: I'm Mikkael Sekeres. I also voted yes. Patients with end-stage multiple myeloma, patients who have been heavily pretreated have few, if any, viable options, and today we voted to make one option available to them. The

response rate was acceptable for this population, and the safety was also acceptable. My great hope is that the potential confirmatory study shows a magnitude of progression-free survival that's at least as good as what we're seeing today. And more importantly, I hope that it will show an overall survival advantage.

DR. WILSON: Wyndham Wilson. I voted yes. I feel that this application fulfilled the criteria for what we should see for accelerated approval, an unmet need, a drug with, I felt given the setting, a good response rate and certainly a very good duration of response. And I, too, felt that the toxicity profile was really very reasonable, given the degree of prior therapy here. And the fact that a phase 3 has already been completed I think is in Onyx's favor.

DR. FREEDMAN: Ralph Freedman. I voted yes for all the reasons that have been given, essentially, and I think it's important that there is a phase 3 trial that's ongoing and one that's due to start in hopes that, for similar situations

in the future, where we have accelerated approval, there will be confirmatory trials that are already activated.

DR. ARMSTRONG: Deborah Armstrong. I also voted for approval. I think the responses are real, and probably, even more important, are meaningful in this population. The confirmation trial, again, not only has been planned but has completed accrual, and there's a second study. Based on these, it's probably moving into an earlier population, and so I don't know that we'll actually get true confirmation in this population ever. But I think based on what's available for these patients, I think this is definitely improving the therapeutic armamentarium in myeloma.

DR. ZONES: I'm Jane Zones, and I voted yes, but I feel queasy about it. I did think that the benefit outweighed the risk here, but I'm very concerned about -- it feels like the data is kind of soft. I'm looking forward to seeing a more -- the phase 3 study. I know it's difficult to carry out this kind of research in this

population, but I'd like to see something that's a little more solid.

DR. OMEL: I'm Jim Omel, and I very happily voted yes for all of the reasons that have been mentioned. I had no reticence or queasiness whatsoever. I think it's a great addition to our armamentarium for myeloma, and it's extremely effective. We can't basically vote on it because of effectiveness, but in first-line patients, it's 100 percent effective. It's a great drug.

Adjournment

DR. WILSON: Okay. Well, I'd like to thank the presenters, the committee, and the meeting is now adjourned.

(Whereupon, at 4:26 p.m., the afternoon session was adjourned.)